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TEMPORARY ARREST OF THE CIRCULATION TO THE CENTRAL NERVOUS SYSTEM

I. PHYSIOLOGIC EFFECTS

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Some years after Harvey's demonstration [1] of the circulation of the blood in 1628, Stenonis [2] (1667) made the celebrated observation that occlusion of the descending aorta produced paralysis of the hindlimbs of dogs. This was the first recorded observation on the connection between the circulation of blood and neuromuscular function.[3] Since then a great deal of work has been done on the relationship between blood flow and neural function. In 1858 Brown-Séquard [4] demonstrated that the cerebrum, medulla oblongata, spinal cord and peripheral nerves were affected in that order by temporary interruption of the blood supply, the cerebrum being the most susceptible to damage and the peripheral nerves the least susceptible. Brown-Séquard also showed that the presence of oxygen in the circulating blood was essential to revive nerve tissue which

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1. Harvey, W.: Exercitatio anatomica de motu cordis et sanguinis in animalibus, Frankfurt, G. Fitzer, 1628.

2. Stenonis, N.: Elementorum myologiae specimen seu musculi descriptio geometrica cui accedunt causis carchariae dissectum caput et dissectus piscis ex canum genere, Florence, Typog. sub signa stellae, 1667, p. 86.

3. Batelli [7] and others have erroneously referred to Swammerdam (Tractatus physico-anatomico-medicus de respiratione usuque pulmonum, Leyden, D. Abraham and A. à Gaasbeeck, 1667, p. 61) as having been the first to make this observation on mammals. Swammerdam explicitly stated that this experiment was demonstrated to him by his good friend Dr. Stenonis.

4. Brown-Séquard, C. E.: Recherches expérimentales sur les propriétés physiologiques et les usages du sang rouge et du sang noir, J. de la physiol. de l'homme **1**:119 and 364, 1858.

had been temporarily deprived of its blood supply. It appears, then, that arresting the flow of blood to nerve tissue produces its effects primarily by interrupting the supply of oxygen. Indeed, Sugar and Gerard [5] have recently shown that the effects of an abrupt interruption of cerebral blood flow "are primarily due to anoxia, but hypoglycemia and especially hypercapnia may well contribute, as also may the increased extracellular potassium induced by anoxia." Extensive reviews on the connection between blood flow and neural function have been published by Hill [6]; Batelli [7]; Pike, Guthrie and Stewart,[8] and Gildea and Cobb.[9] The following discussion will be confined to the methods employed to interrupt the flow of blood to the brain and spinal cord and the results obtained by these methods.

The surest way of completely cutting off the supply of blood to the brain is by division of the neck. This procedure, of course, precludes prolonged survival studies. The method consequently is suitable for little more than the study of the time the lower bulbar centers can withstand interruption of the blood flow. The first observations of this kind were made by Brown-Séquard.[4] He decapitated dogs and inserted cannulas into the carotid and vertebral arteries. Ten minutes after the disappearance of the respiratory movements of the nostrils, lips and lower jaw the head was perfused with blood. Movements of the eyes and face were noted after two or three minutes of perfusion. Hayem and Barrier [10] (1887), using approximately the same method, stated that automatic and reflex movements could not be restored after twelve minutes of cerebral anoxia. Heymans, Jourdan and Nowak [11] perfused the isolated head of a dog by connecting the carotid arteries and jugular veins with those of a second dog. Palpebral reflexes could not be reestablished after the perfusion had been stopped for more than eight minutes, while the respiratory and cardioregulatory centers could be revived after

5.* Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938.

6. Hill, L.: On Cerebral Anemia and the Effects Which Follow Ligation of the Cerebral Arteries, Phil. Tr. Roy. Soc., London, s.B **193**:69, 1900.

7. Batelli, F.: Le rétablissement des fonctions du coeur et du système nerveux central après l'anémie totale, J. de physiol. et path. gén. **2**:443, 1900.

8. Pike, F. H.; Guthrie, C. C., and Stewart, G. N.: Studies in Resuscitation: I. General Conditions and the Resuscitation of the Blood of the Heart, J. Exper. Med. **10**:371, 1908.

9. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

10. Hayem and Barrier: Effets de l'anémie totale de l'encéphale et de ses diverses parties, étudiés à l'aide de la décapitation suivie des transfusions de sang, Arch. de physiol. norm. et path. **10**:1, 1887.

11. Heymans, C.; Jourdan, F., and Nowak, S. J. G.: Recherches sur la résistance des centres encéphalo-bulbaires à l'anémie, Compt. rend. Soc. de biol. **117**:470, 1934.

eighteen minutes of circulatory arrest. In a later paper [12] the authors stated that the respiratory, cardioregulatory and vasomotor centers could be revived and resume their activity after arrest of the circulation for thirty minutes.

Less certain methods of interrupting the flow of blood to the brain have been employed in the intact animal. These methods however, have the virtue of allowing prolonged study of the surviving animal. The technic most frequently used is the temporary clamping or permanent ligature of both carotid and both vertebral arteries. First introduced by Cooper [13] in 1836, it has been used by many workers, including Mayer [14] (1878), Hill [6] (1900), Stewart and his associates [15] (1906), Pike and his associates [16] (1908) and Gildea and Cobb [9] (1930).

The objection to this method is that complete arrest of the cerebral circulation is not obtained because of the collateral circulation. A dog in which Cooper ligated both carotid and both vertebral arteries had convulsions and was stuporous. On the fourth day the dog was almost normal, and it gradually recovered completely. Hill found that in rabbits, cats and monkeys ligation of the four arteries resulted in death immediately, or after the lapse of a few hours. In dogs, on the other hand, the procedure was practically never fatal because of the collateral circulation through the superior intercostal and anterior spinal arteries. Brown,[17] in 1916, completely isolated the head from the trunk of an animal except for the spinal cord and cervical vertebrae. Methylthionine chloride (methylene blue) injected into the cephalic vessels could, however, be detected in the aorta and the internal mammary and intercostal vessels. Chauchard and Chauchard [18] (1928) showed that in the dog there is sufficient collateral circulation through the brain by way of the spinal arteries to maintain the electrical excitability of the cortex when the four

12. Heymans, C.; Bouckaert, J. J.; Jourdan, F.; Nowak, S. J. G., and Farber, S.: Survival and Revival of Nerve Centers Following Acute Anemia, Arch. Neurol. & Psychiat. **38**:304 (Aug.) 1937.

13. Cooper, A.: Some Experiments and Observations on Tying the Carotid and Vertebral Arteries, Guy's Hosp. Rep. **1**:457, 1836.

14. Mayer, S.: Resultate meiner fortgesetzten Untersuchungen über die Hemmung und Wiederherstellung des Blutströmes im Kopfe, Centralbl. f. d. med. Wissensch. **16**:579, 1878.

15. Stewart, G. N.; Guthrie, C. C.; Burns, R. L., and Pike, F. H.: The Resuscitation of the Central Nervous System of Mammals, J. Exper. Med. **8**:289, 1906.

16. Pike, F. H.; Guthrie, C. C., and Stewart, G. N.: Studies in Resuscitation: IV. The Return of Function in the Central Nervous System After Temporary Cerebral Anemia, J. Exper. Med. **10**:490, 1908.

17. Brown, E. D.: Artificial Cerebral Circulation After Circulatory Isolation of Mammalian Brain, J. Pharmacol. & Exper. Therap. **8**:185, 1916.

18. Chauchard, A., and Chauchard, B.: Rôle des collatérales des artères vertébrales et carotides dans l'irrigation de l'écorce cérébrale, Compt. rend. Soc. de biol. **99**:1628, 1928.

major arteries are ligated. Andreyev,[19] in 1935, showed that 60 per cent of his dogs survived ligation of the carotid and vertebral arteries because of a rich anastomotic circulation.

In view of these considerations, it is clear that the effects produced by occlusion of the carotid and vertebral arteries will vary in different species. Even in the same species the effects will vary with the extent of the collateral circulation. Thus, Mayer [14] stated that with interruption of the cerebral circulation for from ten to fifteen minutes respiration and vasomotor activity returned, but voluntary movements or normal behavior was never observed to follow cerebral anemia of this duration. Stewart [15] and Pike [16] and their associates found that cerebral anemia for seven and a half minutes resulted in death in 1 instance, while in another the cat recovered completely after interruption of the circulation to the brain for sixteen and a half minutes. This disparity is in itself testimony to the variability of the collateral circulation. Gildea and Cobb [9] came to the conclusion that ten minutes was the upper limit of duration of cerebral anemia from which cortical cells can recover, and they suggested that even this figure may be too high.

Recently, Kabat and Dennis [20] devised an ingenious technic for interrupting the circulation to the head in dogs. At a preliminary operation the laminas and spinous process of the second cervical vertebra were removed and both vertebral arteries ligated. After one or two weeks a blood pressure cuff was placed about the neck and the pressure in the cuff raised to 350 mm. of mercury, thus occluding the spinal arteries as well as all the arteries in the neck. They were able to revive a dog after nineteen minutes of compression, although the animal remained in coma for nine days, until death. In a recent communication Dennis and Kabat [21] described a modification of their technic by raising the pressure in the cuff to 700 mm. of mercury and reported their results in 6 dogs. In 2 animals with cephalic circulatory arrest for ten minutes there was no return of consciousness, although the animals survived four and six days, respectively. The other 4 animals, subjected to eight minutes or less of cephalic circulatory arrest, recovered consciousness and after ten days showed normal activity except for residual ataxia, which persisted.

Still another method of interrupting the blood flow to the nervous system in an intact animal is to produce general circulatory collapse and

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19. Andreyev, L. A.: Functional Changes in Brain of Dog After Reduction of Cerebral Blood Supply: Cerebral Circulation and Development of Anastomosis After Ligation of Arteries, Arch. Neurol. & Psychiat. **34**:481 (Sept.) 1935.

20. Kabat, H., and Dennis, C.: Decerebration in the Dog by Complete Temporary Arrest of the Cephalic Circulation, Proc. Soc. Exper. Biol. & Med. **38**:864, 1938.

21. Dennis, C., and Kabat, H.: Behavior of Dogs After Complete Temporary Arrest of the Cephalic Circulation, Proc. Soc. Exper. Biol. & Med. **40**:559, 1939.

then to revive the animal. Various means of producing circulatory failure have been employed: electrical shock to produce ventricular fibrillation, chloroform intoxication until the heart beat disappears and exsanguination. Batelli [7] produced ventricular fibrillation by electrical shock and then effected a return to the normal beat by cardiac massage and passage of an alternating current of 240 volts directly through the heart. The period of circulatory arrest was assumed to begin with the fibrillation and to end with the beginning of cardiac massage. He concluded that the limit of duration of cerebral anemia after which resuscitation was possible was in the neighborhood of fifteen minutes.

Crile and Dolley [22] chloroformed dogs and calculated that the period of circulatory arrest began when the first heart sound was no longer audible. The animals were resuscitated with an intra-arterial injection of physiologic solution of sodium chloride and epinephrine, artificial respiration and extrathoracic cardiac massage. The reappearance of heart sounds was taken to indicate reestablishment of the circulation. With this method an animal was restored to normal after as long as seven and a half minutes of apparent death. These authors regarded ten minutes as the maximum period of circulatory arrest from which recovery was possible.

Heymans and Bouckaert,[23] in 1935, produced "clinical" death by hemorrhage or asphyxia. At varying intervals after the disappearance of the heart sounds the animals were resuscitated. The authors were able to reanimate dogs after thirty minutes of "apparent" death, although the animals never regained consciousness and died within twenty-four hours. Heymans and Bouckaert noted that if revival was delayed for more than five minutes the animals exhibited symptoms indicative of cerebral lesions. Winkelbauer,[24] in 1936, bled dogs until "clinical" death occurred, the criterion of which was cessation of heart sounds, respiration and pulse. At this time blood was rapidly reinjected, epinephrine given and artificial respiration started. The resumption of the heart beat was taken to indicate the end of the period of circulatory arrest. Winkelbauer succeeded in restoring an animal after a period of twenty-three and a half minutes, during which the heart sounds were inaudible. However, if the period of apparent death was longer than five or six minutes the dogs suffered irreparable injury. All these various methods which depend on the period of "apparent" or "clinical" death to represent

22. Crile, G. W., and Dolley, D. H.: On the Effect of Complete Anemia on the Central Nervous System in Dogs Resuscitated After Relative Death, J. Exper. Med. **10**:783, 1908.

23. Heymans, C., and Bouckaert, J. J.: Sur la survie et la réanimation des centres nerveux, Compt. rend. Soc. de biol. **119**:324, 1935.

24. Winkelbauer, A.: Experimentelle Untersuchungen über Wiederbelebung nach Verblutung, Deutsche Ztschr. f. Chir. **245**:1, 1935.

the period of circulatory arrest are open to the objection that the method does not necessarily completely stop the circulation of blood, and that the end points are not sharp.

The effect of circulatory arrest on the spinal cord has been studied by a number of investigators, all of whom have used the method of temporary ligation of the aorta. The numerous anastomoses between the intervertebral and the spinal arteries have been the cause of variable results when the abdominal aorta was clamped. This difficulty has been avoided by occluding the thoracic aorta. Colson [25] found that the functions of the spinal cord would not reappear if occlusion of the thoracic aorta lasted more than twenty minutes. Recently, Tureen,[26] also occluding the thoracic aorta, has confirmed Colson's results. He found that motor power did not return to the hindlegs if the occlusion lasted twenty minutes, while all the animals were able to walk within twenty-four hours after a fifteen minute occlusion of the thoracic aorta.

Despite the large amount of information which has accumulated, complete arrest of the circulation to the entire nervous system has not been produced for a definite period in an intact animal with subsequent survival. The length of time that the central nervous system of an intact animal can withstand interruption of the blood flow and the changes that are produced by varying periods of circulatory arrest have not been precisely determined. In endeavoring to obtain answers to these questions the following method was employed.

METHOD

The observations were made on cats. In all experiments the circulation of blood to the entire body was abruptly halted by occluding the pulmonary artery with a clamp. After varying intervals the clamp was removed and the circulation of blood reestablished. The reappearance of blood flow in the retinal vessels was taken to indicate the end of the period of cerebral circulatory arrest.

In the cat the lungs completely overlie the pericardium, and in order to expose the pulmonary artery artificial respiration must be employed, because the left pleural cavity has to be opened. This was an undesirable feature in these experiments, as it precluded the observation of natural respiratory movements. To obviate this difficulty, a preliminary operation was performed six weeks before the experiment. Artificial respiration and anesthesia were maintained by the intermittent insufflation of air and ether vapor through a catheter inserted in the trachea through the mouth. Portions of the pectoralis major and minor muscles overlying the fourth and fifth costal cartilages were removed, and these cartilages, together with bits of the adjacent ribs, were resected. The left pleural cavity was opened through the bed of the fifth costal cartilage and rib. The portion of the peri-

25. Colson: Recherches physiologiques sur l'occlusion de l'aorte thoracique, Arch. de biol. **10**:431, 1890.

26. Tureen, L. L.: Effect of Experimental Temporary Vascular Occlusion on the Spinal Cord: Correlation Between Structural and Functional Changes, Arch. Neurol. & Psychiat. **35**:789 (April) 1936.

cardium overlying the pulmonary artery was then sutured to the margins of the opening in the thoracic wall and the incision in the skin closed. This procedure made it possible about six weeks later to expose the pulmonary artery in a normally breathing animal by merely incising the skin and the underlying pericardium.[27]

Animals prepared as described were used in all the experiments. With the cat under ether anesthesia a catheter was inserted into the trachea through the mouth and connected with a closed rebreathing circuit containing a mixture of ether vapor and oxygen. An even level of anesthesia without anoxemia could be maintained by this method. An incision was made over the site of the previous operation, and the pericardial sac was entered without opening the pleural cavity. By means of a small aneurysm needle the pulmonary artery was separated from the intrapericardial portion of the aorta. A special clamp [28] was then passed around the pulmonary artery. This clamp was so designed that when closed there was no possibility of blood escaping past it. In the excised heart with the clamp in place about the pulmonary artery, it is possible to raise the pressure in the right ventricle almost to the point of rupture (240 mm. of mercury) without forcing any fluid through the pulmonary artery. When these steps were completed, the intratracheal catheter was disconnected from the anesthetic circuit and the animal allowed to breathe room air. When the reflexes were all present and the animal began to struggle against the restraints, the pulmonary artery was rapidly occluded by the clamp. The circulation of blood to the entire body was thus abruptly halted.

From this moment the retina was continuously observed with an ophthalmoscope. Within a few seconds after the pulmonary artery was clamped the arteries of the retina faded from view. The column of blood in the veins broke up into short segments in from thirty seconds to two minutes. These beads of blood in the veins moved slowly toward the optic disk. This motion, which was probably due to the gradual equalization of pressure between the large arteries and the large veins, ceased in from one to three minutes after the pulmonary artery was clamped. During the period of occlusion the retina was pale, the arteries were imperceptible and the position of the veins was indicated only by the small clumps of stagnant erythrocytes. The beading of blood in the retinal veins was regarded by Kahn [29] as a clinical sign of death. Salsbury and Melvin [30] stated that when the movement of these clumps of corpuscles ceases "it seems quite impossible that recovery can take place." In the observations of Gildea and Cobb,[9] some movement of blood in the retinal vessels persisted throughout the period of cerebral anemia.

During the period of occlusion the heart continued to beat feebly but regularly. Electrocardiographic records showed disturbances of auriculoventricular conduction and modification of the QRS complexes. The heart rate became slower, and the right auricle and ventricle became markedly distended. At the end of periods ranging from two to ten minutes, the clamp was quickly unscrewed and removed from the pulmonary artery. Just before the clamp was removed from the artery artificial respiration was begun by the intermittent insufflation of oxygen or room

27. Gibbon, J. H., Jr.: The Maintenance of Life During Experimental Occlusion of the Pulmonary Artery Followed by Survival, Surg., Gynec. & Obst. **69:** 602, 1939.

28. Gibbon, J. H., Jr.: Artificial Maintenance of the Circulation During Experimental Occlusion of the Pulmonary Artery, Arch. Surg. **34:**1105 (June) 1937.

29. Kahn, M. H.: A New Vascular Sign of Death, Am. J. M. Sc. **168:**890, 1924.

30. Salsbury, C. R., and Melvin, G. S.: Ophthalmoscopic Signs of Death, Brit. M. J. **1:**1249, 1936.

air through the intratracheal catheter. At the moment of release 2 minims (0.124 cc.) of epinephrine hydrochloride and 15 cc. of physiologic solution of sodium chloride were injected into the femoral artery toward the heart and cardiac massage was started.

When the circulation returned to the retina the beads of blood in the veins began to move, first slowly and then rapidly. In a few seconds they merged into a solid column of blood and the retinal arteries suddenly sprang into view. The point at which the vessels became filled with blood was taken to indicate the return of the blood flow to the brain. The interval between the release of the clamp and the restoration of the retinal circulation was included in calculating the period

TABLE 1.—*Immediate Effects of Temporary Circulatory Arrest to the Central Nervous System in Nineteen Cats*

		Time After Clamping Pulmonary Artery of						
				Loss of Ophthalmic Reflexes		Onset of Pupillary Changes		
Date, 1938	Experiment No.	Onset of Convulsions, Sec.	Cessation of Convulsions, Sec.	Light, Sec.	Corneal, Sec.	Constriction, Min.:Sec.	Dilatation, Min.:Sec.	Cessation of Respiration, Min.:Sec.
November 1	10	15	30	..	..	....	....	2:15
November 8	11	15	25	..	..	....	....	1:50
November 22	12	..	..	..	25	0:25	1:25	....
December 7	15	..	..	..	..	0:50	....	2:10
December 7	16	..	30	..	..	....	....	1:40
December 15	21A	10	25	..	..	0:50	1:15	2:40
December 15	22	10	40	..	..	....	....	2:15
1939								
January 12	23	..	25	..	..	0:55	1:45	1:40
January 18	24	15	35	..	..	....	1:45	1:30
January 19	25	15	30	..	..	1:00	....	2:25
January 25	26	10	25	..	..	1:05	1:30	1:45
February 1	27	13	30	..	..	0:30	1:30	2:10
February 1	28	8	12	..	..	....	1:25	1:50
February 7	29	12	45	45	45	0:45	1:20	1:25
February 15	30	10	30	..	15	0:20	1:30	1:45
February 22	31	15	35	35	45	1:05	1:45	2:15
February 22	32	17	35	35	35	....	1:30	2:00
March 1	33	20	35	40	47	1:00	1:30	2:10
March 2	34	11	26	35	35	1:00	1:32	2:00
Mean		13	30	35	40	0:53	1:30	2:00

of circulatory arrest. As artificial respiration was started before the release of the pulmonary artery, the blood entering the cerebral vessels was adequately oxygenated. Artificial respiration with oxygen or room air was maintained until spontaneous respirations were resumed, at which time the catheter was withdrawn from the trachea. The parietal pericardium was then loosely approximated with a few interrupted silk stitches, and the skin was sutured.

RESULTS

This experiment was performed on 30 cats, with aseptic precautions. Six of them died at some point in the procedure. The 24 animals which survived either died or were killed at periods of from seventy-five minutes to six weeks after the operation. Table 1 lists the 19 experiments in which two or more of the following observations were made: the onset

and cessation of convulsions, the loss of ophthalmic reflexes, the occurrence of changes in the pupil and the cessation of respiration. Convulsions began almost uniformly in about thirteen seconds after the pulmonary artery was clamped. They lasted from four to thirty-three seconds and were followed by coma and complete flaccidity of the body musculature. The pupillary and corneal reflexes disappeared rapidly and at approximately the same time. This has also been noted by Stewart and his associates [15] and by others. The shortest period of survival of the ophthalmic reflexes was fifteen seconds and the longest forty-seven seconds. The pupils started to constrict in from twenty to sixty-five seconds after the pulmonary artery was clamped. The constriction continued until the pupils were pinpoint in size. They then started to dilate slowly. Dilatation began seventy-five to one hundred and five seconds after the onset of circulatory arrest. The time the respiratory mechanism survived complete arrest of the circulation is indicated in the last column. Though regular respiration almost always ceased when convulsions ceased and in no instance continued for more than forty-five seconds, the cats continued to gasp irregularly for variable lengths of time. The last gasp was taken to represent the onset of paralysis of the respiratory mechanism. The longest period of survival was two minutes and forty seconds, and the shortest, one minute and thirty seconds. When the circulation was stopped for only two minutes (experiments 12 and 13) the gasps generally continued throughout the entire period.

The question naturally arises whether the stagnant blood in the cerebral capillaries may not provide oxygen to the nervous system and thus keep it viable for a time. On the basis of the known respiratory rates of cortical tissue and its capillary as measured by Craigie [31] and Pfeifer,[32] Gerard [33] calculated that stagnant blood could not furnish oxygen to cortical cells for more than ten seconds. The onset of convulsions in approximately thirteen seconds in our animals lends support to this calculated time. Sugar and Gerard [5] found that cerebral cortical potentials disappeared from fourteen to fifteen seconds after the interruption of the cerebral circulation, and that potentials for basal ganglia disappeared in twenty-five to thirty-seven seconds. It is roughly within the same period after the arrest of the circulation that convulsions occurred in the experiments reported here. Convulsions did not occur after the first forty-five seconds of occlusion. On the other hand, Gildea

31. Craigie, E. H.: The Vascularity of the Cerebral Cortex of the Albino Rat, J. Comp. Neurol. **33**:193, 1921.

32. Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

33. Gerard, R. W.: Brain Metabolism and Circulation, A. Research Nerv. & Ment. Dis., Proc. **18**:316, 1938.

and Cobb [9] observed convulsions during the period of occlusion, but some time after the onset of cerebral anemia. The delay in the appearance of the convulsions in their animals may have been due to the fact that the cerebral circulation was not completely arrested.

Restoration of Automatic and Vegetative Functions.—At the end of two minutes and thirty seconds of circulatory arrest, the animals appeared dead. They were completely flaccid and without reflexes. The rectal

TABLE 2.—*Results of Temporary Circulatory Arrest to the Central Nervous System*

Group	Experiment No.	Time Pulmonary Artery Was Clamped, Min.	Period of Cerebral Circulatory Arrest, Min.:Sec.	Time After Reestablishment of the Circulation of the Appearance of			Period of Survival	
				Spontaneous Respiration, Min.:Sec.	Ophthalmic Reflexes			
					Light, Min.	Corneal, Min.	Died	Killed
I	12	2	2:00	Immediately	3	4	.....	1 week
	13	2	2:00	Immediately	..	7	.....	3 weeks
	18	3	3:10	0:40	5	5	.....	1 week
	6	3	3 to 3:10	1:35*	..	..	.....	6 weeks
II	22	3	3:25	0:50	..	..	.....	1 week
	21A	4	4:25	1:05	..	..	.....	.....
	7	4	4 to 5:30	3:30*	..	12*	.....	6 weeks
	20	5	5:40	3:20	..	..	.....	5 days
	21B	4	5:45	2:45	14	17	.....	1 week
III	14	4	6:07	3:48	11	11	5 days	.....
	33	6	6:35	2:30	9	12	.....	2 days
	25	6	6:45	7:15	15	15	.....	6 weeks
	16	6	6:50	3:40	7	14	3 days	.....
	34	5	7:05	7:30	10	13	2 days	.....
IV	31	7	7:36	6:14	9	15	5 days	.....
	17	7	7:45	3:00	12	14	.....	8 days
	8	5	5 to 8:00	7:00*	..	16*	.....	6 weeks
	10	7	7 to 9:00	4:00*	..	21*	5 weeks	.....
V	24	6	8:45	11:25	16	20	6-22 hours	
	23	6	9:00	14:15	..	20	48-51 hours	
	28	9	9:40	16:50	..	58	4-20 hours	
	9	6	6 to 10:00	9:30*	..	22*	26 hours	
	4	5	5 to 10:00	14:30*	..	24*	75 minutes	
	27	8	10:15	15:15	29	22	6-22 hours	
	11	8	8 to 10:30	7:45*	..	21*	30-46 hours	

* These time intervals were calculated from the moment the pulmonary artery was released; the others from the time the circulation was first observed in the retinal arteries.

temperature began to fall, and the animals were cold to the touch. The mucous membranes were pallid and the paw pads bloodless. The cornea was wrinkled, due to the loss of intraocular tension, and no tears were present. After reestablishment of the circulation, color returned immediately to the mucous membranes, and the wrinkled corneas filled out. The blood pressure rose to its preocclusion level, at varying intervals depending on the effectiveness of the restorative procedures and the length of time the pulmonary artery was clamped.

Table 2 summarizes the results of the 25 experiments which were performed with aseptic precautions and in which the animals survived

the procedure. The experiments have been arranged in order of increasing length of circulatory arrest. In addition, they have been divided somewhat arbitrarily into five groups for convenience in discussing the postoperative condition of the animals. One animal (cat 21) was subjected to two periods of clamping the pulmonary artery. Experiment 21B was performed seven weeks after the animal had been subjected to the first period of circulatory arrest (experiment 21A). In 18 of the 25 experiments the period of circulatory arrest was accurately determined by observation of the retinal vessels. In 7 early experiments the retina was not observed. It was difficult to determine the exact place in the table in which these animals belonged. Because the technic for resuscitation was not well developed in the early experiments, the period of circulatory arrest was undoubtedly considerably longer than the time the pulmonary artery was clamped. In these experiments notes were made in the protocols indicating the time at which the heart action was strong or at which a cut artery bled freely. The end of the period of circulatory arrest, then, was judged to be intermediate between this time and the time of release of the pulmonary artery, and is so expressed in table 2. In columns 5 and 7 the time intervals marked with an asterisk indicate that they were calculated from the moment the pulmonary artery was released, whereas all the other figures in these columns were calculated from the time at which the circulation was first observed to return to the retinal vessels.

Respiration always returned before the ophthalmic reflexes. It started as a spasmodic, sobbing gasp, which was followed by gasps at more frequent intervals. The rhythm shortly became regular, and the rate gradually increased. There was no constant relationship between the length of the period of circulatory arrest and the time after restoration of the circulation at which spontaneous respiration reappeared (table 2). In a general way only, the longer the period of circulatory arrest the greater was the delay in the return of respiration. The pupillary and corneal reflexes also returned irregularly, although again the delay in reappearance increased with longer periods of circulatory arrest.

Recovery of Neural Function and Extent of Ultimate Loss.—In order to simplify the account of the condition of the animals following the period of circulatory arrest, the experiments will be discussed under the five groups indicated in table 2.

GROUP 1: Circulatory arrest for two minutes to three minutes and ten seconds.

The 4 cats in this group all began to mew and move their extremities within a few minutes after the conclusion of the operation. All were able to walk by the end of thirty minutes. The hind quarters were weak, and the animals walked with a "string-halt" gait. Decerebrate rigidity and clonic convulsions did not occur. By the end of twenty-four hours the cats appeared entirely normal with respect to both motor power and behavior. Thus the nervous system apparently

tolerates complete arrest of the circulation for periods of three minutes and ten seconds or less without any evident permanent disturbance of function. No difference was noted in the rate of recovery between the animals subjected to two minutes and those subjected to three minutes and ten seconds of circulatory arrest.

GROUP 2.: Circulatory arrest for from three minutes and twenty-five seconds to five minutes and forty-five seconds.

In this group there were 4 animals, 1 of which (cat 21) was subjected to two periods of circulatory arrest. After the experiments the animals lay quietly for twenty to thirty minutes. At the end of this time they began to mew and move their forelegs in running and scratching movements. In 2 experiments (20 and 21B) a position of opisthotonos, with the neck arched back and the forelegs extended, was assumed by the cats in the immediate postoperative period. The animals were frequently excitable, and any stimulus would set them to clawing and dragging themselves about the floor with their forelegs. The hindlegs were weak and spastic and were usually stiffly extended. This paresis of the hindlegs lasted from two to six and a half hours, at the end of which time they were able to struggle to a standing position. Although able to stand, 2 of the animals were not able to walk until the following morning. At the end of twenty-four hours they were able to stand and walk, although the hindlegs showed various degrees of weakness and spasticity. The hopping and placing reactions described by Bard [34] showed marked disturbances, ranging from delay and hypometria to complete absence. The righting reflexes were present, and the animals were able to climb and balance fairly well.

These disturbances of function gradually disappeared, and by the end of a week all the surviving animals were normal so far as motor functions, vision, hearing and sensation were concerned. However, they were no longer active and responsive. They appeared disinterested in their environment and remained in a corner of the cage. If placed out on the laboratory floor they either remained where they were or went to a corner of the room and lay down. They did not purr in response to stroking and could not be induced to play. If they were tormented they did not make an adequate response. They yowled and showed evidence of rage when their tails were pinched but did not bite and claw at the observer's hand. The cats showed no curiosity and were indifferent to barking dogs, but would not tolerate being placed in water.

In this group the disturbances in motor function which immediately followed the operative procedure cleared up rapidly, but the animals showed persistent alterations in behavior and appeared to lack normal intelligence. Gildea and Cobb [9] were the first to emphasize this loss of intelligence, and they regarded it as "an indication of severe disturbance in cortical function." The experiments reported here seem to indicate that in the cat permanent disturbances in cortical function occur after approximately three and a half minutes of cerebral circulatory arrest.

GROUP 3: Circulatory arrest for from six minutes and seven seconds to seven minutes and five seconds.

There were 5 cats in this group. One was killed after two days because of infection of the wound. One died on the third and 1 on the fifth postoperative day. Another cat died two days after operation in status epilepticus. One animal lived and was killed at the end of six weeks. After the operation 4 of the cats lay on the side with the neck hyperextended and the forelimbs rigidly extended. The

34. Bard, P.: Studies on the Cerebral Cortex: I. Localized Control of Placing and Hopping Reactions in the Cat and Their Normal Management by Small Cortical Remnants, Arch. Neurol. & Psychiat. **30**:40 (July) 1933.

hindlimbs were spastic and generally extended also. In 2 animals during the first hour this attitude was punctuated by recurrent tonic spasms that accentuated the posture. Clonic convulsions developed in 2 cats. Cat 34 had repeated short convulsive jerks of the forelimbs and neck, which recurred at intervals until death on the second day. Cat 14 had violent convulsions at the conclusion of the operation. The convulsions were characterized by a tonic onset with extension of the neck and legs. This was followed by a clonic phase in which the animal made violent biting movements, twisting its head from side to side, kicking and jerking with its hindlimbs and flexing and extending its back. Some of the convulsions were so violent as to throw the animal off the table, and a wooden gag had to be placed in the mouth to protect the tongue. After one hour of status epilepticus the violence of the convulsions abated, but convulsive jerks of the forelimbs continued at intervals for two days.

From one to four hours after the operation all the animals exhibited running movements. These could be provoked by pinching the tail or by other painful stimuli. In 4 of the animals there developed intermittent bouts of intense hyperactivity and excitement which did not appear to be accompanied by consciousness. They thrashed wildly about the cage, and if the lid was open they threw themselves out. In the intervals between the bouts of activity, the animals would assume a position of extensor rigidity. The limbs were spastic to passive motion, and hopping and placing reactions were absent.

This hyperactivity, which lasted from two to five hours, was in marked contrast to the condition of the animals the following morning. Twenty-four hours after the experiment the animals were stuporous and indifferent to painful stimulation. Only 1 of them was able to stand. All the animals could move their forelegs, but the hindlegs were paralyzed or markedly paretic. The animals were soiled with excretions, which doubtless accounted for the infection of the wounds. At the time the animals were killed or died all of them (except cat 25) appeared blind, did not react to light flashed in their eyes, dragged themselves off the edge of a table and bumped into objects. Two were unable to stand up. The other 2 animals could stand or crouch but were unable to walk. They fell over on their sides if a step was attempted. On attempting to stand they assumed bizarre postures with their legs crossed or spraddled wide apart. Their extremities could be placed in all sorts of contorted positions, from which they made no effort to extricate themselves (fig. 1). The hopping and placing reactions were either absent or defective. A weak yowl was the only response to painful stimuli. The animals were unable to eat or drink and required feeding by stomach tube.

Cat 25 survived for six weeks. Motor function improved and appeared normal on the ninth day. The cat, however, was obviously blind and remained so until the twentieth day, at which time it was apparent that some vision was returning. The animal ceased to walk off the edge of a table or bump into objects and followed a moving light with its eyes. Its course was one of continued improvement for about five weeks following the experiment, after which time its condition became stationary. At this time all motor functions were normal except that occasionally a peculiar wide-based stance of its hindlegs was assumed. All hopping and placing reactions were normal. The animal balanced and climbed normally. It undoubtedly had defective vision until it was killed, since it could not find its food pan if this was moved a few inches away from its head. It yowled and hissed but would not attempt to escape, bite or scratch if its tail was pinched. It ate voraciously, kept itself clean and would not tolerate being placed in water. It showed little curiosity and would not play, although it purred on one occasion when its fur was stroked with a brush. The acoustic reflexes were extraordinarily acute.

In this group of animals the cells or mechanisms which subserve intellectual function appeared to suffer irreparable injury. In this connection it is interesting to review the observations of Schaltenbrand and Cobb,[35] Bard,[34] Langworthy and Kolb,[36] Bard and Rioch,[37] Barris [38] and Magoun and Ranson.[39] These authors removed the cortex, both frontal lobes or the entire neocortex of both hemispheres by surgical ablation. After the operative procedures their animals showed difficulty in eating and chewing, lack of normal affectivity, inadequate defense reactions, peculiar postural abnormalities, postural plasticity and demented behavior. On the other hand, general locomotion, hearing, smell and sensation do not suffer appreciably from wide cortical ablations. In time the lower motor and extrapyramidal systems compensate for the lack of cortical function. It is possible that the excellent motor recovery in cat 25 was dependent on some such process. The abnormal behavior with permanent visual defect points to widespread and serious functional impairment of the cortex.

The hyperactivity and wild purposeless behavior that occurred a short time after the restoration of cerebral circulation have been observed by others. Gildea and Cobb [9] and Crile and Dolley [22] both mentioned the hyperactivity occurring some time after the period of cerebral anemia. Judging from the typical postures of the animals immediately following the periods of interruption of the circulation to the brain, there appears to be at least temporary decortication, if not decerebration. The tonic spasms also speak for a release of the lower centers from cortical control. The violent motor behavior associated with all the mimetics of rage indicates that cortical function was in abeyance and that the caudal portion of the hypothalamus was still capable of function.[40] With partial recovery of cortical function during the first twenty-four hours, the cat's lower motor and emotional centers are brought under some control. This explanation gains substantiation from the fact that while the hindlegs performed all sorts of movements during the immediate postoperative period, they were almost invariably completely paralyzed on the following day.

Group 4: Circulatory arrest for from seven minutes and thirty-six seconds to seven minutes and forty-five seconds.

There were 4 animals in this group. One died after five days, and 1 was killed at the end of eight days. The other 2 cats survived for weeks. After the operation the animals either maintained a position of decerebrate rigidity or had repeated tonic spasms in which the head arched backward and the extremities stiffened out. They were insensible to stimulation. The respiratory rates were rapid in all the

35. Schaltenbrand, G., and Cobb, S.: Clinical and Anatomical Studies on Two Cats Without Neocortex, Brain **53**:449, 1931.

36. Langworthy, O. R., and Kolb, L. C.: The Experimental Production in the Cat of a Condition Simulating Pseudo-Bulbar Palsy, Am. J. Physiol. **111**:571, 1935.

37. Bard, P., and Rioch, D. McK.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

38. Barris, R. W.: Cataleptic Symptoms Following Bilateral Cortical Lesions in Cats, Am. J. Physiol. **119**:213, 1937.

39. Magoun, H. W., and Ranson, S. W.: The Behavior of Cats Following Bilateral Removal of the Rostral Portions of the Central Hemispheres, J. Neurophysiol. **1**:39, 1938.

40. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928.

animals, often too rapid to count. From one and a half to three hours later, varying degrees of hyperactivity developed. Cat 17 made violent running movements of the forelegs when stimulated. Cat 10 showed spasmodic jerking and running movements of the legs, and later scrambled violently around its cage. Cats 8 and 31 had bouts of wild hyperactivity, thrashing and tumbling about the floor, yowling and tearing at the screen of the cage. Cat 31 displayed typical attacks of "sham rage" when held on its back, similar to those described by Bard.[40] The animal yowled, clawed viciously but aimlessly at the air, lashed its tail, retracted its ears and erected its fur. Its eyes were widely opened and the pupils

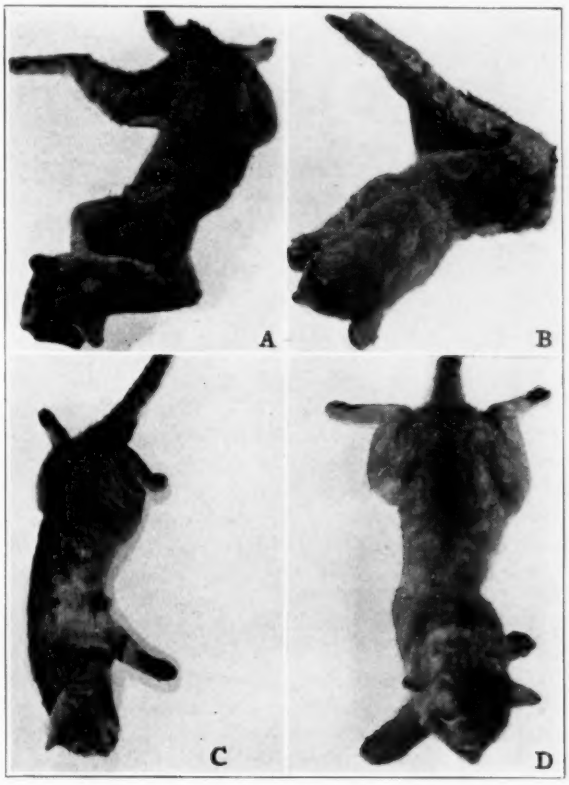


Fig. 1.—Photographs illustrating postural plasticity in cats 33 (*A* and *B*) and 34 (*C* and *D*) forty-eight hours after periods of circulatory arrest of six minutes and thirty-five seconds and seven minutes and five seconds, respectively.

dilated. The tonic neck reflexes which Magnus and de Kleijn[41] noted in decerebrate preparations were also present in this cat. Three of the cats displayed extensor rigidity when they were freely suspended.

At the end of twenty-four hours 3 of the animals were stuporous and unresponsive to painful stimulation. Only 1 animal, cat 17, was able to stand up. The animals were blind, and all had to be fed by a stomach tube. Cat 31 had repeated

41. Magnus, R., and de Kleijn, A.: Die Abbängigkeit des Tonus der Nackenmuskeln von der Kopfstellung, Arch. f. d. ges. Physiol. **147**:403, 1912.

clonic convulsions mingled with tonic extensor fits, and there developed spastic paralysis of the left foreleg, with the wrist acutely flexed. Its back, neck and jaws were extremely spastic, and on the third day gross tremors of the head and legs were noted. The cat remained blind, insensible and spastic, and made only feeble scratching movements until death, which occurred after five days. Cat 17 was able to walk at the end of forty-eight hours, but its hindlegs assumed awkward postures. It improved in motor power, but was never able to feed itself. At the time it was killed it could walk and jump but was not able to climb or balance. Only slight weakness of the hindlegs was observable on walking, and all the hopping and placing reactions were present, though defective and hypometric. Apathy was pronounced, and yowling was the only response to painful stimuli. The cat walked off the edge of a table, bumped into objects and could not find its way out of corners. It would not eat food or lap milk and had to be fed by a stomach tube. It was killed on the eighth day.

Cats 8 and 10 were the most interesting of all the animals. The pulmonary artery was occluded for five minutes in cat 8 and for seven minutes in cat 10. The exact time of cerebral circulatory arrest is not known, as the retina was not observed in these early experiments. Cat 8 was observed for six weeks and cat 10 for five weeks. Cat 8 lay on its side for four days, making running movements and thrashing about. It was fed by a tube during this period. At the end of four days it was able to stand, though often with its legs crossed or in some other unnatural position. On the sixth day it walked, though the hindlegs were weak. From this time it improved, and it was able to lap milk on the seventh day. On the eleventh day the animal was able to swallow solid food if it was placed in its mouth. On the seventeenth day peculiar attacks of rage were noted whenever the animal was stroked. It would hiss and yowl, arch its back into the characteristic "Hallowe'en" attitude, lash its tail and retract its ears. These were noted throughout the period of its survival. On the twenty-third day the condition was apparently static. The cat was obviously blind and had great difficulty in stepping over the smallest obstacles. A very strong light flashed into its eyes elicited a winking reflex, although this has been shown to exist even in surgically decorticated animals.[37] It lapped milk well, but had difficulty in eating solid food. It continued biting at a piece of salmon until its mouth was stuffed. It would keep trying to swallow, the food in the meanwhile dropping out of its mouth. When enough had fallen out, the animal was able to bolt down the remainder. The cat made no effort to clean itself, and its fur was matted and dirty. It would lick the objects held against its mouth. The animal was able to run, and if prodded into jumping it landed with its legs sprawled out. The cat would spontaneously assume queer positions (fig. *2 B*). All extremities were somewhat spastic. When dropped it failed to right itself in midair. Its general behavior varied from complete apathy and immobility to hyperactivity, during which it walked rapidly and restlessly about the laboratory, bumping into objects, tripping and sprawling. It could not get out of a corner if it walked into one. It tolerated being placed in water. When handled an attack of rage was exhibited, but the clawing movements were aimless and it did not scratch or bite the observer. The cat would frequently bite the edge of the food pan and shake it. It turned its head away from noxious odors and salivated freely on inhaling ether, but made no effort to move away. Feeble acoustic reflexes were noted. This condition of blindness, dementia and serious motor and motor reflex disabilities persisted until the cat was killed, at the end of six weeks.

Cat 10 lay on its side, making scratching and stepping movements of its forelegs for a week. It was able to stand on the second day but was unable to walk until the thirteenth day. It was fed by tube for seven days, although it lapped a little milk from the second day. The cat gradually improved with careful nursing during the course of eighteen days. At the end of this time it was totally blind, did not react to light flashed in its eyes and bumped its head into objects. The pupils reacted poorly to light. The animal walked with evident weakness of its hindlegs, and all extremities were spastic. It was unable to stand on a ladder and dropped or sprawled through the bars. It assumed queer standing postures with its legs crossed or sprawled far apart, and it would tolerate having its extremities placed in contorted positions (fig. 2 *E*). Pinching the tail or pricking with pins was generally ignored, although occasionally a feeble mew was elicited.

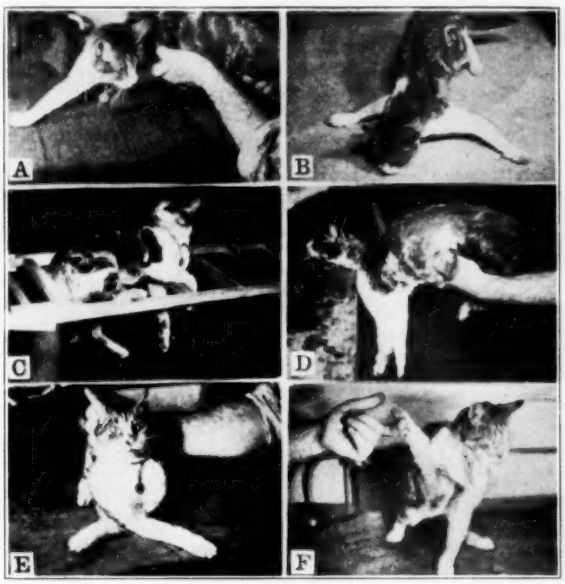


Fig. 2.—Photographs of cat 8 (*A, B, C* and *D*), taken six weeks after circulatory arrest of from five to eight minutes; and of cat 10 (*E* and *F*), taken five weeks after circulatory arrest of between seven and nine minutes. *B, C* and *E* illustrate the postural plasticity. Absence of hopping reaction is shown in *A* and of placing reaction in *D* and *E*.

If tobacco smoke, ether or ammonia was placed under its nostrils, it inhaled these ordinarily noxious odors without the least evidence of awareness. Salivation on exposure to ether vapor did not occur, which strongly suggested that the animal had lost the ability to smell. No acoustic reflexes were elicited by loud sounds. The animal could not find food but would lap reflexly when its snout was placed in milk. It lapped the surface of a piece of salmon but could not bite or chew it even though it was placed in the mouth. The elevation of the tail elicited in normal cats by stroking the back was entirely absent in this cat. It seemed to be completely demented and, except when being examined, sat immobile in the corner of its cage. Put in a corner of the wall or a crevice, it would not find its way out.

If it walked into a wall, it would stop there, unable to solve the problem by turning to one side. Placed in water, it stood unperturbed. At times it would go through long, sustained stereotyped actions, like licking the floor or any object placed against its mouth. At the end of five weeks the animal was no better. It was losing weight, had stopped eating and had to be fed through a stomach tube. It died five weeks after the experiment.

Of this group of 4 cats, 2 (cats 8 and 10) survived for six and five weeks, respectively. Although these animals lived, they were little more than reflex organisms, and even some basic reflex activities were absent. Permanent and irreparable damage was present in such lowly organized cortical functions as smell, vision, hearing and sensation. The impaired placing and hopping reactions indicate damage to the cortex of the frontal lobes.[34] On the whole, these animals exhibited behavioral and motor alterations similar to those observed in surgically decorticated animals. The presence of tremors and other dyskinesias observed in cat 31 strongly suggests involvement of the basal ganglia. The serious defects of chewing in cats 8 and 10 were similar to those noted by Langworthy and Kolb[36] after injury to the rostral portion of the cerebral cortex of cats.

Group 5: Circulatory arrest for from eight minutes and forty-five seconds to ten minutes and fifteen seconds.

There were 7 animals in this group. The shortest period of survival was seventy-five minutes, the longest forty-eight hours. Since their lives were so short after the experiment, each animal will be considered separately.

Cat 24 (eight minutes and forty-five seconds): After the operation the cat lay in coma. Six hours after operation it assumed the typical decerebrate attitude and there developed clonic convulsions superimposed on tonic spasms. The convulsions occurred every ten to fifteen seconds and could be provoked by slight jarring of the animal. Even a loud noise would precipitate a convulsion. No spontaneous movements were made. The animal was found dead the following morning, twenty-two hours after operation.

Cat 23 (nine minutes): The cat remained in coma for four and a half hours. During this time it had extremely violent running movements of its legs, generalized convulsions and tonic spasms. The respiratory rate was over 200 per minute. Twenty-four hours after operation the animal was lying on its side with the forelegs extended against its body and the hindlegs extended stiffly behind it. The cat yowled on stimulation but made no other sign of awareness. The pupils were dilated and reacted poorly to light. At the end of forty-eight hours the animal was stretched out with all four extremities in rigid extension, but it was able to perform feeble phasic movements. The cat was blind and had no acoustic reflexes. The temperature during the two days of its life ranged from 34.8 to 40 C. (94.6 to 104 F.).

Cat 28 (nine minutes and forty seconds): This animal remained in coma, insensible to all external stimuli after the operation. During this time it had severe repeated convulsions every four or five seconds. In an effort to preserve the animal, a small dose of sodium amytal was given to stop the convulsions, three hours after the experiment. The animal was found dead the following morning.

Cat 9: The cat remained in coma until death, at the end of twenty-six hours. Two hours after the experiment bouts of violent running movements of the forelegs occurred, and at the end of three hours the animal assumed a position of opisthotonos with the extremities rigidly extended. Twenty-four hours after the operation it was quieter but was unable to stand. Hopping and placing reactions were absent. Just before death the rectal temperature was 35.1 C. (95.2 F.).

Cat 4: This animal remained in deep coma and perfectly flaccid after the experiment. The respirations gradually failed, and the animal died seventy-five minutes after the operation.

Cat 27 (ten minutes and fifteen seconds): The cat remained in deep coma after the experiment. During the early postoperative period there were tonic extensor spasms and occasional bouts of running movements of the legs. These were followed by repeated convulsions, involving the head and forelegs, until death occurred. The temperature fell to 34 C. (93.2 F.) four hours after the operation. The animal was found dead the following morning.

Cat 11: After the operation the animal assumed a sustained decerebrate attitude and the respirations became very rapid. Twenty-four hours later the animal was lying on its side with the hindlegs rigidly extended and the forelegs held stiffly close to the body. Both forelegs were acutely flexed at the wrist joint. It remained in this position throughout the day, making occasional running movements with its forelegs and mewing. It was found dead the morning of the second day.

With the technic employed in these experiments life could be restored for a short time to cats subjected to more than eight minutes of complete circulatory arrest. One might expect that if the animals could be resuscitated they should live indefinitely with careful nursing. Experience, however, did not bear this out. The same observation has been made by other workers and raises the question of the cause of death. It is possible that secondary failure of the right side of the heart may have been the cause in our animals. Marked distention of the right auricle and ventricle, presumably associated with incompetence of the tricuspid valve, occurs when the pulmonary artery is occluded. However, in all experiments dilatation of the right side of the heart had disappeared before the wound in the chest was closed. At autopsy nothing was seen grossly to account for death. Tureen [26] mentioned that visceral changes took place when the thoracic aorta was clamped for more than fifteen minutes. The period of circulatory arrest employed in our experiments was well under this limit. All animals that had postoperative clonic convulsions died. No explanation of this fact is apparent. Some animals died that did not have clonic convulsions, but none lived that did. The occurrence of tonic spasms did not carry as poor a prognosis.

Bazett and Penfield [42] showed that chronic decerebrate cats lack temperature control. They concluded that temperature control in cats lies "between the level of the middle of the superior colliculi and 2 mm. in front of the pons below and the upper limit of the thalamus above." The low body temperatures observed in some cats in group 5 suggest the possibility of injury extending into this region of the diencephalon. The polypnea which occurred in some of the cats in groups 4 and 5, while indicative of decortication, has been shown by Lilienthal and

42. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain **45**:185, 1922.

Otenasek [43] to be dependent on neural centers or connections lying in the caudodorsal portion of the diencephalon. As these neural centers were still capable of function, at least a portion of the diencephalon was not destroyed by these long periods of circulatory arrest. However, other visceral activities, such as water regulation, intestinal activity and urinary secretion, may have been damaged, as these functions are controlled to a large extent by diencephalic centers.

SUMMARY

The circulation to the entire body can be stopped abruptly and completely by clamping the pulmonary artery. When the pulmonary artery is released, the moment at which the circulation returns to the cerebrum can be determined accurately by observation of the retinal vessels. With this method it is possible to produce severe neurologic disability and still keep an animal alive for long periods. Twenty-four animals were subjected to periods of circulatory arrest, ranging from two minutes to ten minutes and fifteen seconds. Arrest of the circulation for three minutes and ten seconds, or less, was tolerated without any obvious neurologic disturbances. Permanent alterations in behavior and psychic function occurred in animals subjected to three minutes and twenty-five seconds or more of circulatory arrest. After six minutes of circulatory arrest vision and sensation suffered some degree of permanent injury. After seven minutes and thirty-six seconds of circulatory arrest there were permanent and practically complete dementia, blindness, serious sensory and auditory defects, motor and postural defects and reflex abnormalities. When the circulation was interrupted for eight minutes and forty-five seconds or longer, life could not be restored for more than a few hours. In a subsequent paper the pathologic studies on this material will be presented.

43. Lilienthal, J. L., Jr., and Otenasek, F. J.: Decorticate Pylypneic Panting in Cat, Bull. Johns Hopkins Hosp. **61**:101, 1937.

TUBERCULOMA OF THE BRAIN

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Despite the frequency with which tuberculosis attacks the brain, only a small percentage of tumors of the brain disclosed at operation in modern neurosurgical clinics prove to be tuberculomas. Whereas older authors regarded tuberculoma as one of the most common types of cerebral tumor, more modern reports indicate a steadily decreasing incidence, until at present tuberculomas constitute 2 per cent or less of verified tumors of the brain.[1] Several factors have played a role in this reduction. Most important have been the lowered incidence and better treatment of tuberculosis as a disease. Further, there has been a tendency to segregate tuberculous patients in special hospitals and clinics. Finally, there has been prevalent a pessimistic attitude regarding the applicability of surgical measures in the treatment of tuberculoma of the brain, which has doubtless led many surgeons to avoid operating when tuberculoma was suspected. It has seemed worth while to review knowledge of the habits of these lesions and to evaluate the place of surgical methods in their treatment in the light of modern experience. To this end we have surveyed the literature and reexamined the 12 microscopically verified cases of tuberculoma of the brain which have been observed at the Mayo Clinic. In 6 of these operation was performed.

Tuberculosis of the brain is always secondary to a tuberculous focus elsewhere in the body, which need not, however, be clinically active. The tubercle bacilli may reach the brain and its coverings in three fashions. The most obvious and direct route is by the growth of a contiguous lesion. It has been suggested that tubercle bacilli may pass from tuberculous lesions in the nasal and pharyngeal cavities to the cranial meninges by way of the perineural lymphatic channels accom-

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1. Cushing, H.: Intracranial Tumors: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C. Thomas, Publisher, 1932. Heuer, G. J., and Dandy, W. E.: A Report of Seventy Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**: 224-237 (Aug.) 1916. Walshe, F. M. R.: Intracranial Tumours: A Critical Review, Quart. J. Med. **24**:587-640 (July) 1931.

panying some of the cranial nerves. However, no adequate proof of such a migration has been presented.[2] It is generally agreed that the great majority of tuberculous lesions of the brain arise by metastasis via the blood stream from foci which may be confined to one organ (usually the lungs) or may be generalized.[3]

The pathologic characteristics of tuberculosis of the brain are similar to those of tuberculosis in other organs.[4] The tuberculous lesions are the product of the mesodermal tissues—the meninges, the vascular tree and the microglia. The ectodermal elements, the nerve cells and the true neuroglia, play only a passive role and are destroyed by the enlarging tuberculous lesion. A great variety of lesions are found, both focal and diffuse. Bertrand and Médakovitch[5] emphasized their division into tuberculous and nontuberculous types and suggested that many of the atypical lesions will be recognized only if an attempt is made to stain the tubercle bacilli. The present communication is concerned with tuberculomas, which may be defined simply as focal tuberculous lesions, that is, masses of tuberculous granulation tissue. They are to be distinguished from focal nontuberculous lesions, such as tuberculous encephalitis and the true tuberculous abscess of the brain,[6] which resembles in its gross and microscopic structure the abscesses produced by the common pyogenic organisms.

From a clinical point of view tuberculomas may be divided into those which are asymptomatic and those which are associated with clinical evidence of intracranial disease. Most instances of asymptomatic tuberculoma probably escape detection because of a widespread custom of not examining the brain unless the clinical symptoms have suggested that it is the seat of disease, and because small tuberculomas may easily escape any but the most painstaking search. That such lesions constitute a considerable portion of the tuberculomas of the brain is suggested by the data of Lewison, Freilich and Ragins,[7] who found that in 11 of 20 cases of tuberculoma of the brain discovered in the postmortem material of the Cook County Hospital intracranial tuberculosis had not

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2. Krepuska, S.: Primäre Otitis tuberculosa mit Meningitis, Acta oto-laryng. **19**:415-426, 1934.

3. Jaffé, R. H., and Schultz, A.: The Relations Between Tuberculomata of the Central Nervous System and Tuberculous Changes in Other Organs, Am. Rev. Tuberc. **33**:302-312 (March) 1936.

4. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1929.

5. Bertrand, I., and Médakovitch, G.: Etudes anatomiques sur la tuberculose des centres nerveux, Ann. de méd. **15**:419-458 (May) 1924.

6. Buchstein, H. F., and Walsh, M. N.: Unpublished data.

7. Lewison, M.; Freilich, E. B., and Ragins, O. B.: Tuberculoma of the Brain, Ann. Int. Med. **7**:1141-1145 (March) 1934.

been suspected and in only 2 had the symptoms of tumor been produced. Garland and Armitage [8] estimated that in three fourths of cases tuberculomas of the brain are clinically silent until meningitis supervenes.

Tuberculomas associated with the symptoms of intracranial disease may be divided into two groups. In the larger group the symptoms are exclusively or predominantly those of tuberculous meningitis. In these the tuberculomas are more often small and multiple. Because the meningitis itself may produce focal symptoms by invasion and infarction of the brain, it is practically impossible to diagnose the presence of the concomitant tuberculomas. There were 4 cases of this type in our series. In 2 were found, in addition to the basilar meningitis, about thirty-five small tuberculomas of approximately equal size and similar structure lying in all parts of the brain. They had evidently resulted from a shower of tubercle bacilli in the blood stream. In the other 2 cases one and two small chronic tuberculomas of the cerebellum were observed. Tubercle bacilli were found in them only after prolonged search, and it seemed unlikely that they were responsible for production of the meningitis, as postulated by Rich and McCordock.[9]

In a smaller group the symptoms are attributable to the tuberculoma itself. As is true of other types of brain tumor, these may be localizing in character or may be simply indicative of increased intracranial pressure. The remaining portion of this paper will concern itself with this group of tuberculomas, which includes 8 of our 12 cases.

It is important to consider those factors which may determine which of these syndromes—that of meningitis or that of brain tumor—will be present in a tuberculous patient in whom a tuberculoma of the brain develops. A clue to the solution of this problem was provided by Jaffé and Schultz [3] in their recent study of the extracranial tuberculous foci observed in association with tuberculomas of the brain in 46 cases. In 29 cases generalized tuberculosis was present. In 15 instances this had developed during the primary phase of the disease; these patients were all children. In the remaining 14 cases the generalization had presumably arisen from chronic foci in the lungs and lymph nodes; these patients were young adults. Of the patients with generalized tuberculosis 14 had multiple tuberculomas of the brain and 19 had associated meningitis. Fifteen of the patients had only a single extracranial focus, there being no generalization. Of these, only 4 had multiple tuberculomas and only 4 had associated meningitis. The remaining 2 patients had multiple extracranial foci in the absence of generalization. Both had associated meningitis.

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8. Garland, H. G., and Armitage, G.: Intracranial Tuberculoma, J. Path. & Bact. **37**:461-471 (Nov.) 1933.

9. Rich, A. R., and McCordock, H. A.: The Pathogenesis of Tuberculous Meningitis, Bull. Johns Hopkins Hosp. **52**:5-37 (Jan.) 1933.

Nine of the cases in our series have been subjected to a similar study. In 3 cases the only extracranial foci were in the lungs and related lymph nodes; in all these the clinical picture was that of tumor of the brain. In 3 other cases generalized tuberculosis was present; in each of these the clinical picture was that of meningitis. In the remaining 3 cases tuberculous foci were observed in the lungs and in one or more other organs as well. In 2 of these a single tuberculoma was present, producing the symptoms of tumor; in the third multiple tuberculomas and meningitis were present.

The foregoing data of Jaffé and Schultz [3] and our studies suggest that tuberculomas which produce the symptoms of cerebral tumor tend to occur at all ages and in persons who have but a single extracranial tuberculous focus, usually in the lungs or the associated lymph nodes. Tuberculomas that are associated with the clinical picture of meningitis, on the other hand, occur predominantly in the early years of life and in association with generalized tuberculosis. These observations are, of course, to be regarded as trends, and not as fixed rules.

MENINGEAL TUBERCULOMAS

Epidural Tuberculoma; Pachymeningitis Externa Tuberculosa.—Occasionally the pachymeningitis externa accompanying tuberculous caries of the skull will reach such proportions as to produce symptoms by compressing the underlying brain, in which event surgical evacuation of the epidural tuberculoma without incision of the dura is indicated.[10] The bone may be dealt with as in other forms of osteomyelitis.[11] In the experience of one of us (A. W. A.) tuberculous otitis media almost never penetrates the dura to produce generalized meningitis.

Tuberculoma of the Dura.—When the dura is stripped from the brain, masses of tuberculous granulation tissue may adhere to its inner surface. These have been described as "dural tuberculomas," but histologic study shows that the lesions take their origin from the arachnoid and become attached to the dura only secondarily by obliteration of the subdural space. Only rarely will tubercles be found within the dura itself. While the possibility of a tuberculoma arising within the dura cannot be denied, we have not observed such a lesion and believe that they occur but seldom.

Arachnoid Tuberculoma; Chronic Localized Tuberculous Leptomeningitis.—Occasionally tuberculous meningitis remains localized in one region, where are found one or several irregular, firm, grayish white nodules which occupy the subarachnoid space and invade or indent the

10. Sorrel, E., and Malgras, P.: Tuberculome sus-dure-mérien, Bull. et mém. Soc. nat. de chir. **60**:1412-1416, 1934.

11. Adson, A. W.: The Treatment of Cranial Osteomyelitis and Brain Abscess, Ann. Surg. **108**:499-519 (Oct.) 1938.

brain, and which are usually attached to the dura over at least part of their surface. Their gross appearance strongly suggests that of a meningioma. Histologically, the tumor nodules consist of dense masses of connective tissue, in part hyalinized, in which are embedded few or many fairly typical tubercles. Caseation may be absent and is rarely prominent; calcification has been noted. Few tubercle bacilli are to be found. Where the tumor has broken through the pia the brain is softened, and an increased number of perivascular histiocytes and microglia cells are present.

At times these arachnoid tuberculomas attain a considerable extent, yet do not become thickened. The resulting broad, flat tumor has been called a tuberculoma en plaque. Von Czirer [12] described a spectacular case of this sort in which the tumor measured 8.5 by 5.5 cm. and was 0.5 cm. thick. Pardee and Knox [13] reported a similar lesion in the American literature.

Arachnoid tuberculomas have been found most often in young adults. They almost always lie over the convexity of a hemisphere in the region of the central (rolandic) sulcus. As a result, they present a fairly characteristic clinical syndrome consisting of jacksonian seizures of sensory or motor type, followed in time by sensory and motor paralysis of the affected extremity. Finally generalized convulsions and signs of increased intracranial pressure appear. The clinical course is usually chronic and may extend over several years. Death may result from the development of meningitis, from increased intracranial pressure or from other tuberculous lesions.

The differential diagnosis of these lesions from other tumors of the rolandic area, principally meningiomas, rests on the demonstration of a tuberculous focus elsewhere in the body. Laboratory studies are of no assistance. The cerebrospinal fluid, in the absence of generalized meningitis, will contain no tubercle bacilli and will have a cell count little, if any, above normal.

Arachnoid tuberculomas have been regarded as relatively favorable subjects for surgical treatment by either extirpation or simple decompression. Foerster [14] reported having operated in 9 cases of such tumors in four years, with cure or improvement in 5. Two of these tumors are included in our series; both were successfully removed. Tumors of this type must be handled differently from meningiomas in that they must be excised with a margin of surrounding brain tissue.

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12. von Czirer, L.: Ueber eine seltene Form von Hirnhauttuberkulose, Zentralbl. f. allg. Path. u. path. Anat. **25**:152-155 (Feb. 28) 1914.

13. Pardee, I., and Knox, L. C.: Tuberculoma en Plaque, Arch. Neurol. & Psychiat. **17**:231-238 (Feb.) 1927.

14. Foerster, O.: Circumscripte tuberkulöse Meningitis, Berl. klin. Wchnschr. **48**:404 (Feb. 27) 1911.

CASE 1.—Motor jacksonian seizures, which were initiated by paresthesia of the right hand, developed in a woman aged 28 while she was undergoing sanatorium treatment for pulmonary tuberculosis. After almost three years the development of paresis of the right arm, headaches and difficulty in speaking caused her to come to the Mayo Clinic. She presented clinical and roentgenographic evidence of quiescent bilateral pulmonary tuberculosis. Her right upper extremity was weak, and discriminative sensation was impaired. Roentgenograms of the skull and the usual routine laboratory studies of the urine and blood all gave results within normal limits. The sputum contained no tubercle bacilli. At operation in May 1923, a pinkish, granulomatous tumor, about 5 cm. in diameter, was observed to be adherent to the inner surface of the dura in the left rolandic area. It was removed in one piece, with a margin of brain tissue. The patient made a good recovery from the operation. In 1926 a flare-up of her pulmonary lesion necessitated a



Fig. 1 (case 1).—Photomicrograph (van Gieson stain; × 5½) of a section of an arachnoid tuberculoma, showing an almost normal dura and a thick mass of collagenous fibrous tissue occupying the enlarged subarachnoid space beneath it. Extension of the tuberculous process along a fissure into the brain is seen at the lower edge of the field.

second period of sanatorium care, but there were no symptoms referable to a cerebral lesion. In 1928 convulsive seizures recurred, but there was no evidence on reexamination of an expanding intracranial lesion, and the seizures were controlled with sedatives. In September 1932, nine years after operation, the symptoms and findings of diffuse tuberculous meningitis developed rapidly and led to the patient's death in a month.

The operative specimen presented the appearance of a chronic lesion (fig. 1). Tubercle bacilli were observed, in specially stained sections. The postmortem specimen presented the typical picture of tuberculous basilar meningitis. The site from which the tuberculoma had been removed nine years previously showed

a less intense reaction than was visible in many other parts; there was nothing which could be described as a recurrent tuberculoma.

CASE 2.—A woman aged 35 had had left motor jacksonian seizures for two months. General physical, neurologic and ophthalmoscopic examination revealed nothing of note except slight weakness of the muscles of the left side of the face. Routine laboratory studies, including roentgenograms of the skull, gave normal findings. An encephalogram had been made elsewhere and was said to have shown a filling defect of the right lateral ventricle. Several of the patient's relatives had died of tuberculosis. At operation a tuberculoma similar to that in case 1 was removed from the right rolandic area. A letter received nine months later stated that the patient was well and free from seizures. The histologic structure of the lesion was essentially similar to that described in case 1, except that over much of its extent the tumor had not penetrated the pia (fig. 2).

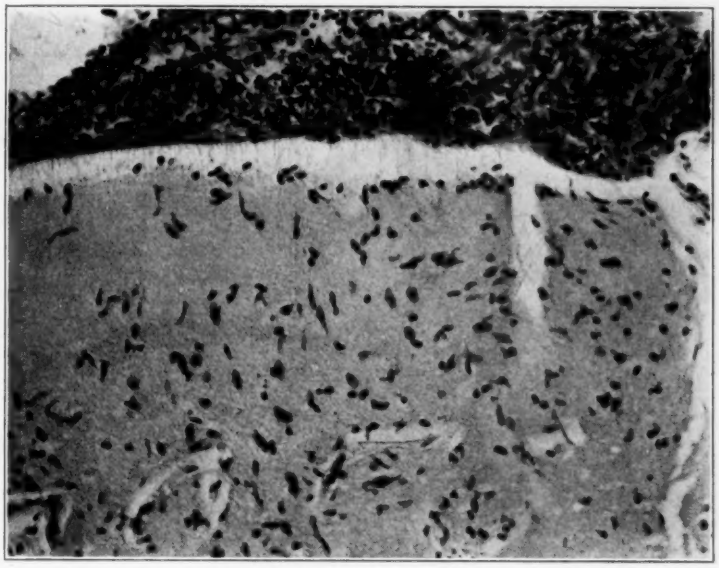


Fig. 2 (case 2).—Photomicrograph (hematoxylin and eosin; × 170) showing numerous rod (microglia) cells in the subpial cortex beneath an arachnoid tuberculoma.

FIBROCASEOUS (INTRAENCEPHALIC) TUBERCULOMAS

By far the most commonly encountered form of tuberculoma of the brain is a circumscribed mass of firm granulation tissue containing typical tubercles, the central portion of which has undergone caseous necrosis, lying chiefly or wholly within the substance of the brain. To distinguish them from the meningeal tuberculomas and to indicate their situation, they might be termed intraencephalic tuberculomas, just as those of the spinal cord are commonly called intramedullary tuberculomas. However, it seems best to retain the most descriptive of the terms in common use, namely, fibrocaseous tuberculoma, and to add to this qualifying adjectives. Thus, one may speak of solitary fibrocaseous tubercu-

lomas if their shape approximates that of a spheroid or ovoid; or of conglomerate fibrocaseous tuberculomas if their outline is irregular and nodular as though formed by the fusion of several solitary tuberculomas, as indeed they are. Rarely the central portion of a fibrocaseous tuberculoma becomes softened. Its semifluid content is not true pus, and the lesion is to be distinguished from the true tuberculous abscess of the brain.[6] Occasionally a fibrocaseous tuberculoma becomes calcified. In 11 (1.35 per cent) of 815 cases collected by Scott and Graves,[15] the tuberculoma was noted to be calcified.

Most fibrocaseous tuberculomas are less than 2 cm. in diameter, but they may be much larger. Tuberculomas of the cerebral and cerebellar

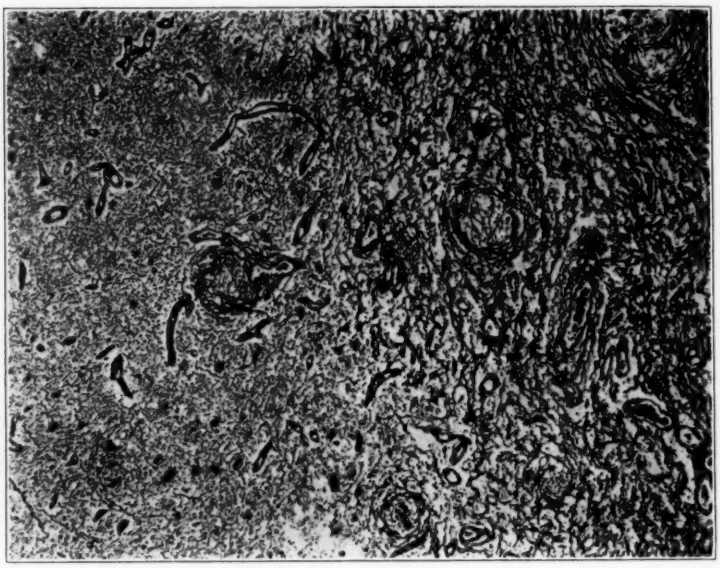


Fig. 3 (case 3).—Photomicrograph (Perdrau stain; × 55) of a section of the periphery of the fibrocaseous tuberculoma removed in case 3. The fibrous structure of the lesion and the extreme vascularity of the border zone are well shown. A perivascular tubercle is seen in the brain tissue just beyond the limits of the tuberculoma.

hemispheres are more likely to reach the surface and adhere to the meninges than are those of the brain stem. It is typical of fibrocaseous tuberculomas that they separate easily from the brain tissue in which they are embedded. The surrounding brain is frequently noted to be hyperemic, even as viewed in the fresh gross specimen.[16] It is usually

15. Scott, E., and Graves, G. O.: Tuberculoma of the Brain with a Report of Four Cases, Am. Rev. Tuberc. **27**:171-192 (Feb.) 1933.

16. Grinker, R., and Lifvendalh, R. A.: A Study of Cerebral Tuberculomas, Arch. Neurol. & Psychiat. **20**:415-416 (Aug.) 1928.

stated that tuberculomas destroy a volume of brain equal to their own; this is not strictly true, however, and various degrees of deformity of the brain result from the presence of a tuberculoma. This may produce internal hydrocephalus and increased intracranial pressure.

The silver staining methods (Perdrau) illustrate particularly well the structure and manner of growth of fibrocaseous tuberculomas. They show the tuberculoma to be an essentially fibrous structure. The fibers, at first reticular and later collagenous, are products of the perivascular mesodermal elements and microglia. The border zone between the tuberculoma and the brain is characterized by its conspicuous vascularity. This has been described as proliferation of new vessels,[17] but we find no evidence for such a process. Rather, it seems that the capillaries already present in great abundance have hypertrophied. In the vicinity of the tuberculoma in some instances numbers of reactive (ameboid) astrocytes may be seen, but in no case did we observe any glial fibrosis about a tuberculoma. In every case we proved the identity of the tuberculoma by finding in specially stained sections one or more acid-fast bacilli.

Certain peculiarities of cerebellar tuberculomas deserve mention, as they may have a bearing on the therapeutic problem. Owing to the depth to which the interfolial septums of pial tissue penetrate the cerebellum, almost every tuberculoma will be in contact with such septums at one or more points. In actively growing tuberculomas the inflammatory process may be seen to extend along these sheets of mesodermal tissue far beyond the ostensible limits of the tumor. Thus, what appears to be complete removal of such a tuberculoma will usually actually be incomplete. Furthermore, if the inflammatory reaction extends to the arachnoid about the lower end of the fourth ventricle obstructive hydrocephalus may result, which will not be relieved by removal of the main tumor.

Statistics based on a large series of cases of fibrocaseous tuberculomas [15] indicate in summary that these lesions are as frequently observed pathologically during the first decade of life as during all the years thereafter; that they occur twice as frequently in men as in women; that in two thirds of cases but a single tuberculoma is observed; that while tuberculomas may be present in any part of the brain, they occur as frequently in the posterior cranial fossa as in the entire supratentorial region, and that only in 20 per cent of cases do they lie near or in contact with the surface of the cerebral convexities. When only the tuberculomas which have produced the symptoms of cerebral tumor are considered, they will be found to be as frequent during adolescence and young adult life as during childhood.

17. Zanetti, G.: Sulla struttura ed istogenesi del tubercolo encefalico, Riv. di pat. e clin. d. tuberc. **2**:537-573, 1928; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **52**:88-89, 1929.

It is notorious that a correct etiologic diagnosis is seldom made in cases of tuberculoma of the brain. In 12 of Garland and Armitage's cases the diagnosis was tumor of the brain, but in only 1 was a tuberculoma suspected. Of our series of 6 cases in which operation was performed, the tuberculous nature of the tumor was postulated in 3. In 2 instances the diagnosis was based on the presence of active tuberculosis elsewhere in the body, which, as Dandy [18] has noted, is the basis on which the differentiation of tuberculoma is usually made. A history of tuberculous disease (pleuritis, peritonitis or adenitis) should suggest the possibility of a tuberculoma, but in our experience this warning signal is frequently disregarded. In the only case in our series in which a tuberculoma of the brain occurred in a child, the diagnosis was correctly made on the finding of a positive tuberculin reaction. Such a reaction would not be significant beyond the tenth year. It is frequently stated that tuberculomas are characterized by a febrile course, but we have not found this to be a constant sign or one of differential diagnostic value.

Most tuberculomas of the brain are characterized by a short and progressive course, which has been variously estimated as having an average duration of from two [8] to six months [19] from the onset of symptoms. Occasionally, however, a tuberculoma may pursue a slowly progressive, or even a relapsing, course. That tuberculomas may even heal completely was noted years ago by Horsley.[20] In 1 instance reported a calcified tuberculoma had presumably been present for fifty-eight years.[21]

When a tuberculoma becomes sufficiently calcified it will be visible in roentgenograms of the skull. Ström [22] described the typical appearance of a calcified tuberculoma as a calcified sphere with fenestrated walls containing specks and streaks of calcium, these having a tendency to arrange themselves in a concentric fashion. Cushing observed, in a series of roentgenograms, the appearance of calcium in a tuberculoma of the cerebellum which had been treated by decompression but had not been removed.

Examination of the cerebrospinal fluid has not proved of value in the differentiation of tuberculomas from other tumors of the brain. In

18. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, pp. 384-388.

19. Paulian, D., and Bistriceanu, I.: Contribution à l'étude anatomo-clinique des tuberculomes intracraniens, Paris méd. **1**:429-433 (May 11) 1935.

20. Horsley, V.: Discussion on the Treatment of Cerebral Tumours, Brit. M. J. **2**:1365-1369 (Dec. 23) 1893.

21. Smith, R. P.: Large Calcified Tuberculoma of Cerebrum with Independent Terminal Cerebral Haemorrhage, J. Path. & Bact. **30**:583-585, 1927.

22. Ström, S.: Ueber die Röntgendiagnostik intrakranieller Verkalkungen. Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:577-601, 1919-1920.

the absence of generalized meningitis, cell counts ranging from normal to as high as 140 lymphocytes per cubic millimeter have been reported, the higher counts being in cases of cerebellar tuberculoma. The sugar content of the fluid is normal, and no tubercle bacilli are to be found. Laboratory examinations of the blood are equally useless as differential criteria.

The first attempt at extirpation of a tuberculoma of the brain was undertaken by Hahn [23] in 1880, three years prior to the famous operation of Godlee. In spite of the accumulated experience of the ensuing years, opinion is still divided as to the proper place of surgical methods in the treatment of these lesions. Cushing advised simple decompression followed by general medical measures, particularly for cerebellar tuberculomas, which constituted the lesion in the majority of his cases. He also noted that tuberculomas are not always easy to identify when exposed at operation and mentioned 2 cases in which a supposed tuberculoma proved on removal to be an ependymoma and a xanthoma, respectively. On the other hand, supposed meningiomas and astrocytomas had proved to be tuberculomas. Dandy, on the other hand, expressed the opinion that decompressions are practically useless and recommended complete removal of solitary lesions by wide excision. Rasdolsky [24] concluded that superficial tuberculomas should be extirpated to minimize the danger of meningitis. Parker [25] has recently noted that simple decompression often results in the amelioration of symptoms.

Those who oppose attempts at surgical extirpation of tuberculomas of the brain point out that such lesions are often multiple and frequently lie in inaccessible regions (brain stem); that even though the tuberculoma is removed the patient still has tuberculosis in another organ which may lead to his death or which may give rise to further lesions of the brain; that attempts at removal of the tuberculoma may precipitate fatal meningitis, and that since healing does occur in cases of tuberculoma attention should be directed toward the treatment of the tuberculosis as a disease and the promotion of its healing.[16] Those who favor surgical measures, at least for some tuberculomas, note that in the cases in which operation is performed the tuberculoma is usually single; that operations may successfully be undertaken at times even though the patient has active pulmonary tuberculosis; that worth while results frequently follow extirpation of tuberculomas, and that what at first appears to be a

23. Wernicke, C., and Hahn, E.: Idiopathischer Abscess des Occipitallappens durch Trepanation entleert, Virchows Arch. f. path. Anat. **87**:335-344 (Feb. 4) 1882.

24. Rasdolsky, I.: Tuberkulome des Gehirnes, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:18-31, 1935.

25. Parker, H. L.: Diseases of the Nervous System in Ireland: Some Observations and Comparisons, Proc. Staff Meet., Mayo Clin. **12**:492-493 (Aug. 4) 1937.

tuberculoma may prove to be a benign type of neoplasm. It might also be noted that even though the patient may eventually die of tuberculosis a period of relief will be as welcome as it is to the patient harboring an incurable malignant neoplasm.

Examination of the reported cases of surgical extirpation of tuberculoma of the brain reveals a striking difference in the results, depending on the site of the lesion. This difference has not been emphasized by most authors, but deserves consideration in the formulation of a policy of treatment. Tuberculomas of the brain stem obviously cannot be removed, and decompressive operations will not relieve the obstructive hydrocephalus which they produce. They are essentially fatal lesions. Two of our cases were of this class; in 1 instance a cerebellar decompression was done, without benefit.

With regard to tuberculomas of the cerebellum the situation is almost equally discouraging. Owing to technical difficulties imposed by the location and the structural peculiarity of cerebellar tuberculomas previously mentioned, few of these lesions have been completely removed. Subtotal removals are followed within weeks or months by tuberculous meningitis, and in most cases of "complete" removal the fate is similar. An outstanding exception is the case of Frazier, since Kwan [26] reported the patient to be living after eleven years. The best results seem to have been obtained by Cushing's procedure of suboccipital decompression followed by measures directed toward healing the lesion. The application of this plan is made difficult by the fact that many lesions will not be recognized until they have been exposed or even removed. The 2 cases of cerebellar tuberculoma in our series were not exceptions to the rule. Both patients recovered from the immediate effects of operation—subtotal removal in 1 case, total removal in the other—only to succumb to tuberculous meningitis more than a month later.

It is the group of tuberculomas which lie near or adjacent to the surface of the cerebrum that offers the greatest possibility of cure by surgical excision. Not only are these accessible to complete removal, but in the event they lie near the central sulcus, as most of them do, they produce symptoms which will permit their diagnosis before they have reached too great a size and before generalized meningitis complicates the problem.[27] We have collected reports of 21 cases of complete surgical excision of tuberculomas of the cerebrum since Van Wagenen's paper,[28] that is, during the past decade. Only 1 patient was reported to

26. Kwan, S. T.: Tuberculoma of the Brain, with Report of a Case Eleven Years After Operation, Arch. Neurol. & Psychiat. **22**:1093-1094 (Nov.) 1929.

27. Roger, H., and Poursines, Y.: Le tuberculome cortico-rolandique, Rev. de méd., Paris **52**:239-271, 1935.

28. Van Wagenen, W. P.: Tuberculoma of the Brain: Its Incidence Among Intracranial Tumors and Its Surgical Aspects, Arch. Neurol. & Psychiat. **17**: 57-91 (Jan.) 1927.

have died after operation. Six others had died at intervals varying from eleven to twenty-four months—2 of tuberculous meningitis, 3 of pulmonary tuberculosis and 1 of a second tuberculoma of the brain. The rest were reported to be alive after periods of observation extending up to nine years. While it is true, as Van Wagenen noted, that there is a natural tendency to report only successful results, these reports indicate that the results of removal of cerebral tuberculomas are frequently worth while. In the case of this type in our series, the tumor was successfully removed and the patient remained well for two years, when she died of acute increased intracranial pressure of uncertain origin, but without gross recurrence of the tuberculoma.

CASE 3.—Three months after an attack of pleurisy with effusion, a woman aged 26 began to have jacksonian motor seizures, starting in her left hand. She was pregnant at the time. After delivery of a normal child, headaches and diplopia appeared. Tenderness on percussion in the right frontoparietal region was noted. There were no neurologic abnormalities except weakness of the right external rectus muscle. Choked disk was present bilaterally. Roentgenograms of the chest and skull and the usual tests of the blood and urine all gave findings within normal limits. The spinal fluid was normal in composition and contained 1 cell per cubic millimeter. A firm fibrocaseous tuberculoma of the brain, measuring 8 cm. in its greatest diameter, was removed from beneath the right arm area (fig. 3). The patient made a rapid recovery from the operation and led an active life for two years, when she died at her home of acute increased intracranial pressure. The pathologist reported to us that he found "no evidence of tuberculosis of the meninges or elsewhere in the brain."

SUMMARY

Tuberculomas of the brain occur at all ages and in a variety of types. With a few exceptions, they arise by hematogenous metastasis from a tuberculous focus elsewhere in the body, usually in the lungs or related lymph nodes. Clinical and pathologic studies indicate that tuberculomas producing the symptoms of tumor of the brain develop most frequently in adolescents and young adults with a single extracranial tuberculous focus. Tuberculomas associated with tuberculous meningitis tend to occur chiefly in children and in the presence of generalized tuberculosis. The pathologic characteristics of tuberculomas are not different from those of tuberculosis elsewhere. Tuberculomas may be positively identified by finding acid-fast bacilli in them.

Tuberculomas constitute only a small and declining percentage of verified tumors of the brain. The clinical syndromes which they produce are not significantly different from those produced by other varieties of cerebral tumor. A correct etiologic diagnosis is made only when the patient has active tuberculosis in another organ or in the presence of a positive tuberculin reaction in a child. A history of tuberculous disease in the past is suggestive but not conclusive. Laboratory studies do not

aid in the differential diagnosis. Calcified tuberculoma must be considered in the differential diagnosis of calcified intracranial masses noted in the roentgenogram.

The treatment of tuberculomas of the brain must be directed against tuberculosis as a disease, as well as toward the removal of the local lesion if possible. Experience has shown that attempts at removal of cerebellar tuberculomas almost always end in disaster, owing to the development of tuberculous meningitis. Decompressive operations may afford relief until healing can take place. Fibrocaseous tuberculomas of the cerebrum and arachnoid tuberculomas, particularly those in the rolandic region, form the best subjects for surgical extirpation. They produce symptoms permitting early diagnosis and are accessible to removal in one piece. Good results will follow in a gratifying percentage of cases.

STUDIES IN DYSTROPHIA MYOTONICA

III. EXPERIMENTAL STUDIES IN MYOTONIA

ABE RAVIN, M.D.

DENVER

Interest in myotonia dates from Thomsen's [1] description of the disorder as it occurred in himself and many members of his family. In 1886 Erb [2] crystallized knowledge of myotonia in a monograph describing the behavior of the myotonic muscle following voluntary contraction and following mechanical and electrical stimulation. Little has been added to Erb's complete description of the reaction of the myotonic muscle to electrical stimulation (usually referred to as "electrical myotonia"). The response of the myotonic muscle to mechanical stimulation ("mechanical myotonia") has not yet been thoroughly investigated. As a result mainly of ergographic and kymographic studies, knowledge of the characteristics of myotonia associated with voluntary contractions ("voluntary or active myotonia") has greatly increased since Erb's time. Through the years, also, the effects of many drugs on voluntary myotonia have been studied.

In Thomsen's disease, or myotonia congenita, the myotonia is associated with muscle hypertrophy. After Thomsen's report, cases were described in which the myotonia was associated with atrophy instead of hypertrophy. In 1909 [3] it was recognized that the cases of atrophy represented a separate disease, to which the name dystrophia myotonica was later given.[4] As judged from the numerous descriptions in the literature, the phenomenon of myotonia is identical in the two diseases. It is reported that one of the patients described in Erb's monograph was later found to have dystrophia myotonica.

From the Department of Medicine, University of Colorado School of Medicine and Hospitals.

1. Thomsen, J.: Tonische Krämpfe in willkürlich beweglichen Muskeln in Folge von ererbter psychischer Disposition (Ataxia muscularis?), Arch. f. Psychiat. **6**:702, 1876.

2. Erb, W.: Die Thomsen'sche Krankheit (Myotonia congenita): Studien, Leipzig, F. C. W. Vogel, 1886.

3. Batten, F. E., and Gibb, H. P.: Myotonia Atrophica, Brain **32**:187, 1909. Steinert, H.: Ueber das klinische und anatomische Bild des Muskelschwundes der Myotoniker, Deutsche Ztschr. f. Nervenh. **37**:38, 1909.

4. Curschmann, H.: Ueber familiäre atrophische Myotonie, Deutsche Ztschr. f. Nervenh. **45**:161, 1912.

The purpose of this report is to describe experimental studies of voluntary myotonia made on 10 patients with dystrophia myotonica. A sensitive method for determining quantitative changes in myotonia was devised, and the characteristics of voluntary myotonia and the effect of drugs on voluntary myotonia were studied.

CHARACTERISTICS OF VOLUNTARY MYOTONIA

METHODS

The 10 patients studied have been described in a previous article of this series.[5] Voluntary myotonia was limited to the hand grasp in most patients; in a few it occurred also in the legs. On 5 patients ergographic studies were made of the movements of the thumb. The thumb was chosen rather than one of the fingers for the following reasons: (1) In some patients, as a result of extensive atrophy of the muscles of the forearm, only the contractions of the thumb were sufficiently strong to show myotonia clearly; (2) the movements of the thumb, being in one plane, were recorded more accurately; (3) the forearm and hand could be completely and easily immobilized. The movements of the thumb were adduction-opposition and abduction-extension. The muscles involved in adduction-opposition were mainly the adductor pollicis and the opponens pollicis; the flexor pollicis longus and flexor pollicis brevis may have played a small part. Abduction-extension was performed by the combined actions of the abductor pollicis longus and abductor pollicis brevis and the extensor pollicis longus and extensor pollicis brevis. Myotonia occurred on adduction-opposition of the thumb but not on abduction-extension, which was weak in every case. As regards the myotonic contractions, therefore, adduction-opposition constituted contraction, and abduction-extension, relaxation.

The movements were recorded by means of an ergograph and a kymograph. The extent of the contraction was limited by an adjustable screw. To the ergograph was added a device by which, when desired, part of the weight lifted on contraction could be made to catch at the height of the contraction, so that relaxation was aided by only that part of the weight which slightly exceeded the amount needed to overcome the resistance of the rider of the ergograph. In the experiments on the effect of changes in temperature, the forearm and hand were immobilized in a water bath kept at a constant temperature, and the thumb was connected with the ergograph by a system of pulleys.

RESULTS

1. *Persistence of Contraction After Cessation of Voluntary Effort.*—It was evident in every patient that the muscular difficulty consisted of inability to relax rapidly and easily muscles which had been contracted. Since relaxation is a passive process depending on subsidence of the state of contraction and the presence of an outside extending force, myotonia is actually abnormal persistence of the state of contraction. So far, however, as relaxation ordinarily occurs on the cessation of voluntary effort, it is convenient to speak of a delay of relaxation in myotonia.

Some contractions were only slightly prolonged; others lasted 55 seconds. Only occasionally did a contraction persist at its full extent for even a short time. When the myotonia was marked, relaxation was sometimes slow from the start

5. Waring, J. J.; Ravin, A., and Walker, C. E., Jr.: Studies in Dystrophia Myotonica: II. Clinical Features and Treatment, Arch. Int. Med., to be published.

(fig. 1 *A*). More frequently a period of fairly rapid relaxation was followed by a period during which the contraction subsided more slowly (fig. 2). The initial period often appeared to be normally rapid, and a sudden catch with angle formation would occur at the start of the slower period (fig. 2). The curve of slow relaxation was smooth at times (fig. 1 *A*) and steplike at others (fig. 1 *C*).

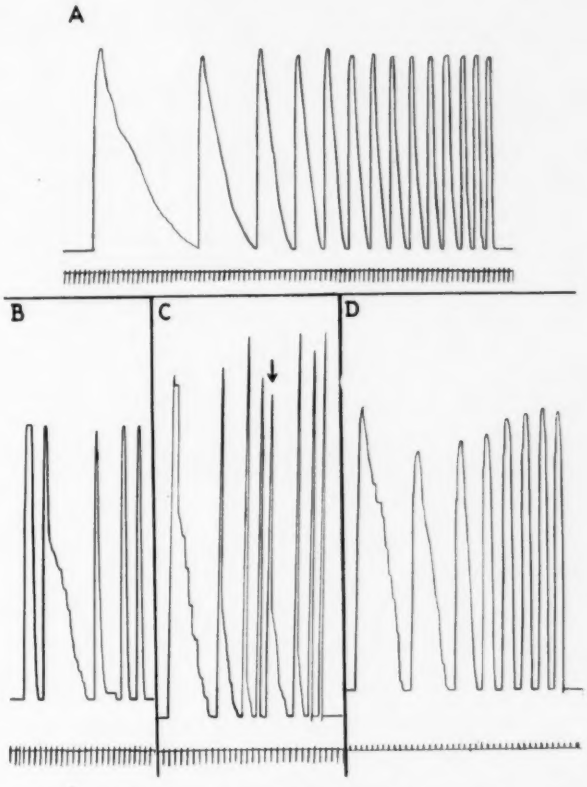


Fig. 1.—*A*, decrease in myotonia with repetition of contraction. Patient M; time expressed in seconds; 100 Gm. weight. Contraction of the myotonic muscles (adduction-opposition of the thumb) is indicated by the upstroke; relaxation, by the downstroke. In obtaining this curve, as all the accompanying curves, the patient contracted and relaxed the thumb on command, so that the curves show the manner and speed of contraction and relaxation but not the speed with which contractions could be repeated.

B, increase in myotonia on second contraction. Patient B; 100 Gm. weight.

C, return of myotonia with increase in force of contraction. Patient P. In the fourth contraction against a 100 Gm. weight the myotonia is no longer apparent. On the fifth contraction (indicated by the arrow) 200 Gm. was added, and the presence of myotonia is again apparent.

D, decrease in height of the second contraction. Patient P. Succeeding contractions show a gradual increase in height. Slowness of the phase of contraction is evident. Contraction was against a 750 Gm. weight; relaxation was aided by only 150 Gm.

Myotonia was associated with a subjective feeling of stiffness, but never with pain.

2. *Decrease with Repetition of the Contraction.*—In every patient repetition of a contraction associated with myotonia resulted in a decrease of the myotonia, so that each succeeding contraction was carried out more easily and rapidly, until no evidence of myotonia could be detected (fig. 1). In cases of very mild type the myotonia was gone after one or two contractions; in cases of more marked disease progressive improvement occurred for twenty or more contractions. A more

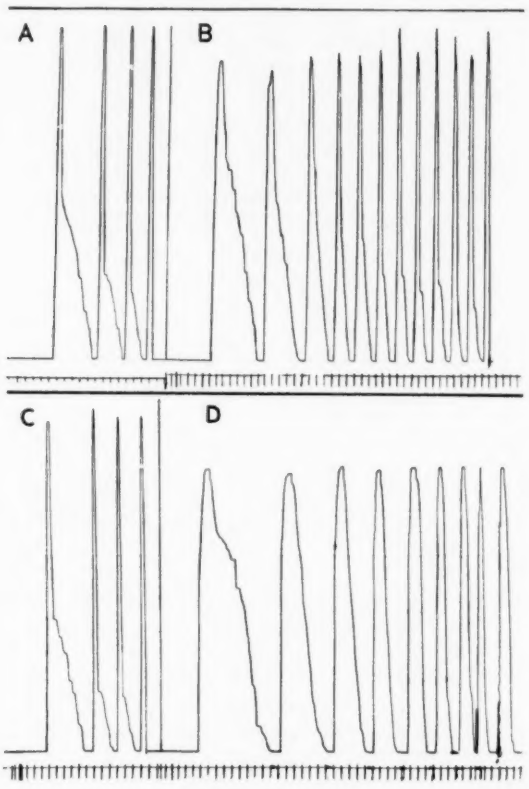


Fig. 2.—Effect of force of contraction on myotonia. Adduction-opposition of thumb. Patient P; time expressed in seconds. The degree of myotonia (seen in the curves as the time taken for relaxation [downstroke]) in *B*, in which the contraction (upstroke) was against a 250 Gm. weight, is much greater than it is in *A* and *C*, in which the contraction was against a 100 Gm. weight. It is still greater in *D*, in which a 600 Gm. weight was used. In all cases relaxation was aided by only 100 Gm. to avoid the error of a variable extending force. All curves show the decrease in myotonia with repetition of the contraction. *D* shows the prolongation of the phase of contraction which occurs with heavier weights.

sensitive method of recording the contractions might have detected a residue of myotonia even after repeated contractions.

An apparent exception to this characteristic was occasionally seen. Although the myotonia was generally most severe on the first contraction, curves were obtained occasionally in which the myotonia increased for one or two contractions before improving. The possibility that the increase in myotonia in the second contraction shown in figure 1 *B* was the result of an increased force of contraction (see next section) could not be entirely ruled out, but observations of the patient and examination of the curve of contraction seemed against this explanation.

Decrease of myotonia with repetition of contraction does not appear to be a fatigue phenomenon, because the myotonia is gone long before fatigue sets in and the strength of contraction increases after the myotonia disappears. The decrease of myotonia appears to be more closely related to those changes which are associated with what is usually called "warming up."

Myotonia which has disappeared because of repeated contractions returns with rest. The more completely the contractions have been freed of myotonia the longer is the rest required for the return of the myotonia to its original level. By experiment it was found that ten minutes sufficed to restore the myotonia lost by the execution of four contractions of the thumb. Similarity of tracings made

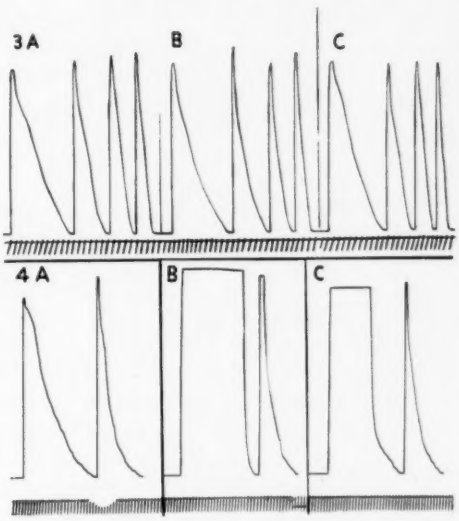


Fig. 3.—Return of myotonia with rest. Patient M; 100 Gm. weight; time expressed in seconds. *A, B* and *C* were taken at approximately ten minute intervals and show the return of the myotonia to the original level after a rest of ten minutes. The time required for the downstrokes of the first three contractions in each set is found to be 24 seconds in *A*, 24¾ seconds in B and 24¼ seconds in *C*.

Fig. 4.—Dual nature of myotonic contractions. Patient M; 200 Gm. weight; time expressed in seconds. *A, B* and *C* were obtained at ten minute intervals. In *A*, relaxation (downstroke) was attempted as soon as contraction was completed. In *B* the thumb was held contracted for a time approximately equal to the duration of relaxation in *A*. The relaxation is rapid almost to the base line, and the total duration of the contraction is equal to that in *A*. In *C* the thumb was held contracted for about half the duration of relaxation in *A*. Relaxation occurs rapidly to the point where the curve would have been if, as in *A*, relaxation had been started immediately; from that point it follows a course similar to that in *A*.

by groups of four contractions at ten minute intervals is shown in figure 3. The importance of this observation is at once evident; standard tracings can be obtained at ten minute intervals and the effect of various procedures and drugs determined.

3. *Variation with Force of Contraction.*—In figure 2 is seen the increase in myotonia which results from increasing the force of contraction. This behavior of myotonia was evident in every case. Myotonia may not be apparent in weak contractions of muscles which show myotonia with stronger contractions. Above a certain limit, which varied for different patients, increase in force of contraction no longer resulted in an increase in myotonia. With the increase in myotonia the number of contractions required to overcome the myotonia was increased. When the myotonia was apparently gone with weak contractions, it became evident again with stronger contractions. Figure 1 *C* shows the effect of adding a 200 Gm. weight after the myotonia was no longer evident on contractions against a 100 Gm. weight.

4. *Dual Nature of Voluntary Myotonic Contractions.*—One of the most interesting and instructive characteristics of myotonia is shown in figure 4. In 4 *A* the thumb was contracted and an attempt made to relax it immediately; relaxation required 22 seconds. In figure 4 *B* the thumb was voluntarily held contracted for 19 seconds, and then relaxation was attempted; relaxation occurred rapidly almost to completion, an additional 3 to 4 seconds being required for complete relaxation. In figure 4 *C* the thumb was held contracted for 13 seconds before relaxation was attempted; relaxation occurred rapidly for a while and then slowly, requiring about 10 seconds for completion. When *A* and *C* of figure 4 are compared, furthermore, it is evident that the level at which the rapid phase of relaxation in *C* changes to the slow phase is the level at which relaxation would have occurred if it had been started immediately after contraction, as in *A*, so that the final portions of the curves can be superimposed. The total durations of the three contractions are thus the same. Apparently, two components are superimposed in a myotonic contraction: one, a voluntary contraction of the usual type, starting and stopping as desired by the will; the other, a persisting contraction setting in at the time of the voluntary contraction and lasting for a definite time regardless of the duration of the voluntary component. Since the same results were obtained when the muscle was made to contract so forcibly that it may be assumed all the fibers were involved in tetanic contraction, it follows that the persisting contraction probably involves the same fibers as the tetanic contraction. The changes in the muscle associated with the persisting contraction, or myotonia, set in and run their course even if the myotonia is obscured by the tetanic contraction. An important point is that myotonia sets in only when the muscle contracts and not during maintenance of the contraction; the nerve impulses produce myotonia when they cause contraction of the muscle and not when they maintain tetanic contraction. The production of myotonia depends, apparently, on the occurrence of those changes in the muscle which are associated with the actual contraction or shortening of the muscle. If the voluntary contraction is prolonged beyond the point at which the myotonia has run its course, no new myotonia sets in and relaxation is rapid, showing that the failure to produce myotonia is not due to a refractory phase. On the other hand, if the voluntary contraction is relaxed at a point at which myotonia is still present and the muscle is contracted again, a new increment is added to the myotonia.

5. *Slow Phase of Contraction.*—Slowness of the phase of contraction, such as was observed by Jensen,[6] was recorded on many occasions (figs. 1 *D* and 2 *D*).

6. Jensen, P.: Zur Analyse der Muskelstörung bei der Thomsen'schen Krankheit, Deutsches Arch. f. klin. Med. **77**:246, 1903.

It was most likely to occur when heavy weights were used and was usually absent with small weights, but a marked variation existed in the weight required at different times. Since in normal persons strikingly similar curves of slow contractions are sometimes obtained with heavy weights, care must be used in evaluating the phenomenon. That this slowness of contraction is a significant finding in myotonia seems possible from the following observations: It occurred with weights comparatively much smaller than those required in the case of normal muscles; it was markedly accentuated by calcium, and it was accentuated by cold (see "Effect of Temperature"). The effect of cold is evident to a slight degree in the curves shown in figure 5 and is striking in some of Nylin's [7] curves.

6. *Decreased Strength of Second Contractions.*—Figure 1 *D* is representative of a number of curves obtained from 2 persons. It shows clearly a decrease in strength of the second contraction and improvement in the third and following contractions. Such curves are best obtained when heavy weights are used, possibly because any weakness which occurs is made more evident and also because a greater degree of myotonia is obtained. An apparent weakness in the second contraction of a myotonic muscle will result if the antagonist of that muscle is also myotonic. The first time the muscle contracts it does so against no resistance, but after the antagonist has contracted the muscle must contract against the resistance of the myotonia now present in the antagonist. In the person from whom figure 1 *D* was obtained, however, attempts to demonstrate voluntary myotonia in the extensor muscles were unsuccessful. The type of curve differs, moreover, from those in which the second contraction is weak because of myotonia in the extensor muscles.

7. *Effect of Circulatory Changes.*—If, as pointed out, groups of four contractions are repeated at ten minute intervals, similar curves are obtained (fig. 3). By altering the conditions during the execution of one of the groups of four contractions, any change due to the altered conditions can be determined by comparison with the other groups. In 3 patients venous congestion produced by placing on the arm a cuff at a pressure of 50 mm. of mercury five minutes before and during the execution of a group of four contractions did not change the character of the curves; the degree of myotonia shown in the first curve was as great as in the controls, and the diminution of myotonia with the repetition of the contraction occurred at the same rate. This result differs from that of Bremer and Mage,[8] who reported that venous congestion decreased the myotonia. It also differs from that of Johnson and Marshall,[9] who stated that both ischemia and congestion caused lengthening of the contraction. In my 3 patients, cutting off the circulation from the extremity by keeping the arm cuff at a pressure above the blood pressure for one and a half minutes before and during the contractions produced no deviation from the controls. In 1 patient, cutting off the circulation for the entire ten minutes between tests did not affect the return of the myotonia. These results

7. Nylin, G.: Two Cases of Dystrophia Myotonica, Type "Batten-Steinert-Curschmann," with a Graphic Investigation of Their States of Contraction and the Influence of Temperature Thereon, Upsala läkaref. förh. **31**:329, 1926.

8. Bremer, F., and Mage, G.: Etude myographique d'un cas de myotonie, Compt. rend. Soc. de biol. **102**:336, 1929.

9. Johnson, W., and Marshall, G.: Observations on Thomsen's Disease, Quart. J. Med. **8**:115, 1915.

suggest that the return of the myotonia is not closely dependent on the state of the circulation.

8. *Effect of Temperature.*—Experiments to determine the effect of immersion of the hand and forearm in water at 20 and 40 C. were performed on 2 patients. In 1 patient, who had only a slight degree of myotonia, little objective difference in the myotonia was noted at 20 as compared with 40 C., although the patient subjectively felt that the myotonia was less at 40 C. The other patient, who was more myotonic, showed less myotonia at 20 than at 40 C. in each of four experiments (fig. 5). Table 1 shows the results of two experiments in which the curves

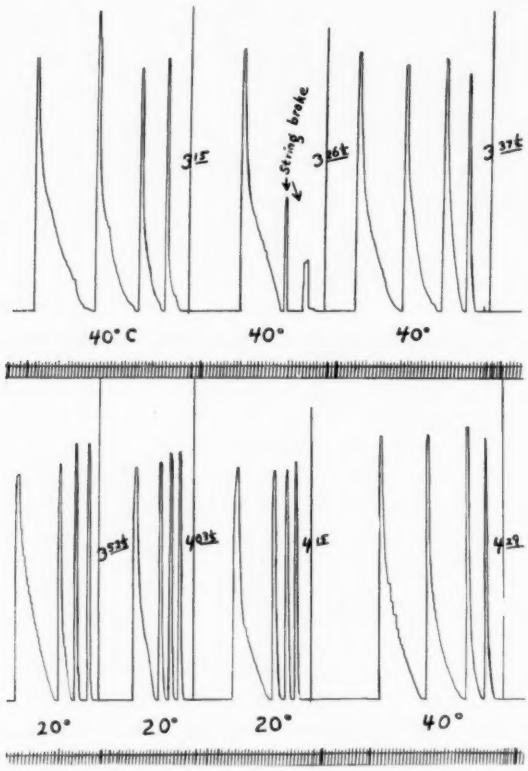


Fig. 5.—Effect of cold on myotonia. Patient M; 100 Gm. weight; thumb movements; time in seconds. The upper three groups of curves were obtained at ten minute intervals with the forearm and hand in a 40 C. water bath and show a fairly constant degree of myotonia. The first three lower groups were obtained at ten minute intervals with the arm and hand in a 20 C. water bath and show a definite decrease in myotonia. When a 40 C. bath was again used (last group), there was an increase of myotonia to approximately the previous level.

were good enough to permit quantitative evaluation. Along with the decreased duration of the phase of relaxation was found an increased duration of the phase of contraction. The patient's sensations are indicated by her statement that with the bath at 20 C. "it felt as though a weight had been added," and with the bath at 40 C.

"it was easier to bring the weight up and more difficult to relax." In this experiment, then, the myotonia was decreased by cold, and the phase of contraction was prolonged and associated with a feeling of weakness.

This result is surprising in view of the almost invariable statement of patients that their muscular difficulty is increased in the cold. The same result, however, was obtained by Nylin,[7] as inspection of his curves shows. Interpretation of these results is difficult. They are not sufficient to refute the general opinion that cold aggravates myotonia, but they do indicate that, although it may be true that cold usually aggravates myotonia, factors may come into play at times which produce a decrease of myotonia with cold. A more thorough investigation of the effect of cold is probably indicated. Questioning of patients reveals that it may be weakness and numbness, rather than myotonia, which cause difficulty in the cold, and it is possible that these patients are mistaking an increase in muscular difficulty due to weakness for an increase in myotonia.

The effect of cold in the experiments described could have resulted from direct cooling of the muscles, which has been shown to occur.[10] The observations on

TABLE 1.—*Effect of Temperature on Myotonia* *

	Date	No. of Groups of Contractions	Temperature, C.†	Average Total Relaxation Time, Sec.‡
Experiment 98	4/14/37	3	20	12
		3	40	20¾
		2	20	7¾
Experiment 99	4/20/37	2	40	30¼
		3	20	12
		2	40	20

* Groups of four contractions were taken at approximately ten minute intervals.
† The temperature of the water bath was changed in the order given.
‡ The "total relaxation time" of a group of four contractions is obtained by determining the time required for relaxation in each of the first three contractions and totaling the results.

the limited effect of circulatory changes on myotonia tend to rule out a reflex vasoconstrictor factor as the cause.

EFFECT OF DRUGS ON VOLUNTARY MYOTONIA

METHOD OF INVESTIGATION

Experiments were performed on 6 patients, on 3 of whom extensive investigations were carried out. The patients were placed in the apparatus described and the contractions of the right thumb recorded. A quantitative measure of the degree of myotonia was obtained by having the patient perform four complete contractions and relaxations and measuring on the kymograph record the time required for relaxation in each of the first three contractions. The sum of these three "relaxation times" was called the "total relaxation time" for the group of four contractions. Groups of four contractions repeated at approximately ten minute intervals for as long as two hours showed nearly the same degree of myotonia. This is well shown in table 2, in which the curves obtained are analyzed on the basis of the "total

10. Bazett, H. C., and McGlone, B.: Temperature Gradients in the Tissues of Man, Am. J. Physiol. **82**:415, 1927. MacLeod, J. J. R., and Taylor, N. B.: Effects of Hot and Cold Applications to the Surface of the Body on the Temperature of the Muscles, Liver, Kidneys and Brain, Lancet **2**:70, 1921.

TABLE 2.—*Total Relaxation Times for Controls*

Experiment No.	Patient	Control Period: Total Relaxation Time (Sec.) at Successive 10 Min. Intervals			Drug Administered	Total Relaxation Time (TRT), in Seconds, and Interval (M), in Minutes, After Injection of Drug											
						TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M
2	P	13¼	13¾	12¾	Distilled water, 0.1 cc. subcutaneously	12¾	5	13½	16	13	26						
5	P	11½	13	13	Distilled water, 0.1 cc. subcutaneously	13½	5	13½	16	14	26	13¼	37	14½	47		
10	P	10¾	9	9	Distilled water, 0.1 cc. subcutaneously	8	5	9	15	9	26	9¾	37	8	47	10	58	8¾	68
17	M	14	13¾	14¼	Distilled water, 0.1 cc. subcutaneously	17	5	16	16	14½	26	13½	37	13½	47				
37	P	17¾	16	15	Ringer's solution, 10 cc. intravenously	16	1	15¾	12	13¼	22	14¾	33	16¼	43				
72	M	....	39½	34	Distilled water, 0.1 cc. subcutaneously	44	5	37	16	35½	27								
29	M	25	27¼	25¾	Distilled water, 0.1 cc. subcutaneously	25¼	4	21¼	15	20¾	27	22	38	21	49				

relaxation time," because it varied less in the controls than the relaxation time of any one curve. Tests made at intervals of longer than ten minutes showed no further significant increase in myotonia. To determine the effect of a drug, tests were made at approximately ten minute intervals; after from two to four tests, which served as controls, the drug was administered and the tests were continued until the effect of the drug had worn off or the fatigue of the patient prevented further tests.

To obtain good results by this method it was essential to avoid (1) variations in the force of contraction, (2) diversion of the patient's attention and (3) changes in the position of the hand. Since myotonia varies with the force of contraction, uniform contractions were essential. Wandering of attention produced jerky and incomplete relaxation curves and a variation in the force of contraction. Changes in the position of the hand were most likely to occur as a result of the additional effort during relaxation, when the myotonia was marked. Training of the patient was important in overcoming these sources of error. Since in an ideal test contraction would be just strong enough to lift the weight and would extend only to the stop screw and relaxation would be carried out smoothly, it is evident that most of the sources of variation tend to produce an apparent or a true increase in myotonia. High figures are therefore occasionally obtained for one or more tests in a control series; variations downward are less common.

Results obtained by taking the patient out of the apparatus and later returning him for continuation of the experiment show variations due partly to inability to duplicate exactly the position of the hand and the extent of contraction and partly to general body changes which do not significantly affect brief experiments but in the longer experiments produce variations which cannot be completely evaluated. With recognition of the presence of such a variation, however, the results obtained by this method can be cautiously interpreted and some conclusions drawn.

RESULTS

Control Experiments.—Table 2 shows that the injection of distilled water did not affect the degree of myotonia.

Epinephrine.—In each of the 6 cases in which epinephrine was tried it produced a decrease in myotonia. The results obtained with the 3 patients on whom kymograph records were made are given in table 3; in 3 other patients a similar improvement was observed but not recorded. Examination of table 3 shows that after the subcutaneous injection of epinephrine (fig. 6) a decrease in the myotonia was evident in from 5 to 10 minutes. It reached its greatest extent in from 15 to 25 minutes and was practically gone in from 45 to 60 minutes. After intravenous injection (table 3; fig. 7) the decrease in myotonia was most evident in from 7 to 12 minutes and was gone in from 25 to 35 minutes. In patients P and B, in whom the myotonia was of slight degree, the effect of the epinephrine was much more evident than in patient M, who had marked myotonia. The decrease in myotonia produced by epinephrine was approximately the same regardless of the degree of myotonia. When the myotonia was slight, the improvement was sufficient to dissipate completely the myotonia (fig. 7). When the myotonia was marked, the improvement, although still of about the same degree, was not as evident and could be easily overlooked. In patient M the improvement present in the early experiments was not sufficient to be evident to her when she was questioned as to whether any change had resulted from the injection. Later, when she was taking quinine orally and the myotonia was greatly reduced but still present, the improve-

ment following an injection of epinephrine was much more evident, not only on the graphs but to the patient. In this patient the effect of the epinephrine was so much more evident after the use of quinine that the production of special sensitization to the action of epinephrine by the quinine was suspected, but could not be verified.

In view of the relative independence of venous congestion and ischemia which myotonia shows, it seems unlikely that the effect of epinephrine on myotonia is produced by a circulatory change. Depending on the size of the dose and the stage in its action, epinephrine can apparently increase or decrease the blood flow to the skeletal muscles. It is highly improbable that epinephrine could have produced

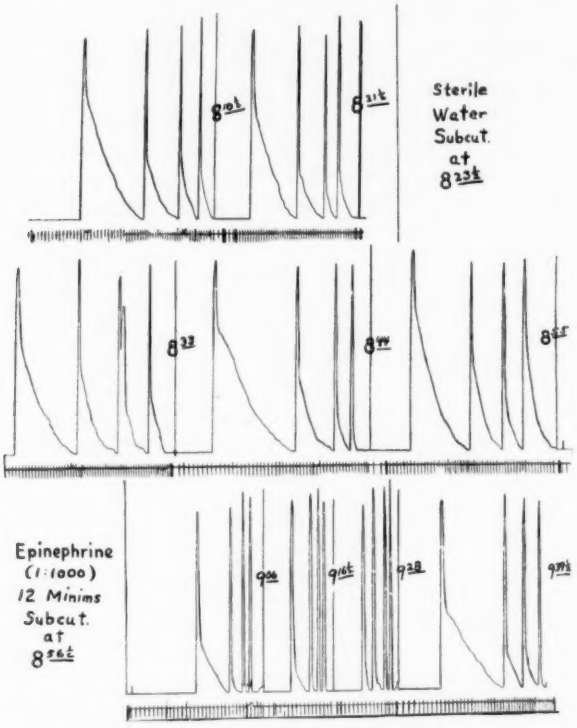


Fig. 6.—Effect of epinephrine on myotonia. Patient M; thumb movements; 100 Gm. weight; time expressed in seconds (note varying speed of kymograph drum).

After the two groups of curves in the upper row were taken, sterile water was injected subcutaneously. The three groups of curves in the middle row show that the sterile water produced no effect on the myotonia. Twelve minims (0.744 cc.) of epinephrine hydrochloride was then injected subcutaneously, with marked effect (lower row).

its marked effect in patient P by decreasing the circulation to the myotonic muscles, for in this patient the absence of circulation for the ten minutes between tests did not prevent the return of myotonia. Improvement of the circulation as a cause of the decrease in myotonia appears to be excluded by the results in experiments 51

TABLE 3.—*Total Relaxation Times After Injection of Epinephrine Subcutaneously and Intravenously*

Experiment No.	Patient	Control Period: Total Relaxation Time (Sec.) at Successive 10 Min. Intervals			Administration of Epinephrine Hydrochloride (1:1,000)	Total Relaxation Time (TRT), in Seconds, and Interval (M), in Minutes, After Injection of Drug											
						TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M
8	P	11½	13	11¾	12 minims (0.744 cc.) subcutaneously	8	7	6	17	4½	28	8½	38	9½	49	10¼	59	10¾	70
9	P	11¾	10	9½	12 minims subcutaneously	7	5	3	15	3½	25	6¾	36	7	48	9¼	58	11	69
16	P	10	9¼	8¾	12 minims subcutaneously	8¼	3	2¾	13	3	24	....	..	7½	45	8½	55		
18	P	15	13½	15¼	12 minims subcutaneously	13½	5	13½	16	10¼	27	10½	37	14¼	48	12¼	58		
20	P	12¾	11¼	12¾	Subcutaneously	11	6	5	16	4	27	8	37	7½	48				
24	M	31½	30½	29¾	8 minims (0.496 cc.) subcutaneously	28	5	25	16	25¾	26	27¼	36						
25	M	26¼	25¾	25¼	12 minims subcutaneously	23	6	21	17	21¾	28	22¾	39	23¼	50	23¼	61		
32	M	36½	33½	34	15 minims (0.93 cc.) subcutaneously.	30½	4	22¾	15	30¼	26	32¾	37	33¾	48				
38	P	18¾	16	14¼	14 minims (0.868 cc.) subcutaneously	4¼	8	1¾	20	4¼	30	7¼	41	13¾	51	16	62	18	73
43	M	....	46¾	52½	14 minims subcutaneously	47	9	25½	20	40	31	50½	44	48½	55	(after quinine)			
*44	M	64	75½	67	12 minims subcutaneously	48½	10	30½	21	18½	32	37½	44	56	54				
47	M	....	34¾	35¼	12 minims subcutaneously	31	4	11½	15	9½	27								
55	B	....	13¼	12½	11 minims (0.682 cc.) subcutaneously	8¼	9	4¼	19	8½	30								
56	B	....	19¼	18¾	10 minims (0.62 cc.) subcutaneously.	15½	10	12¼	20	14¾	31								
57	B	23¼	21½	20¼	12 minims subcutaneously	7¾	8	2	19	2½	30								
69	M	....	37	35½	12 minims subcutaneously	12	9	5½	20	4	31	28	42						
71	B	....	8¾	9¼	12 minims subcutaneously	2¼	7	2½	24	7¼	35	8¾	46						
51	P	14½	14¼ n.c.*	15	12 minims subcutaneously	9¼	9	8	20	5½	31	9¾	41						
						n.c.*		n.c.*											
52	P	13½ n.c.*	11¼	14½ n.c.*	14 minims subcutaneously	10	10	3	20	5	31								
						n.c.*		n.c.*		n.c.*									
33	P	10½	10½	10¼	1½ minims (0.093 cc.) intravenously	9¾	1	1¾	12	8	22	10	33						
30	M	22½	21¾	23	1½ minims intravenously	22¼	3	26	13	20½	25	17	36	20½	47				
70	P	....	10	10½	1½ minims intravenously	1½	7	6½	18	11	28								

* n.c. indicates no circulation for one and a half minutes before and during test.

and 52 (table 3). In these experiments the circulation was stopped for one and a half minutes before and during the performance of the tests marked "n.c." (no circulation). It is evident that no significant change occurred in the effect of the epinephrine as a result of ischemia. These considerations indicate that changes in circulation play a minor part, if any, in the improvement in myotonia which follows the injection of epinephrine.

Figure 8 illustrates an experiment to determine a possible central effect of the epinephrine.[11] When the blood pressure cuff was used to stop the circulation

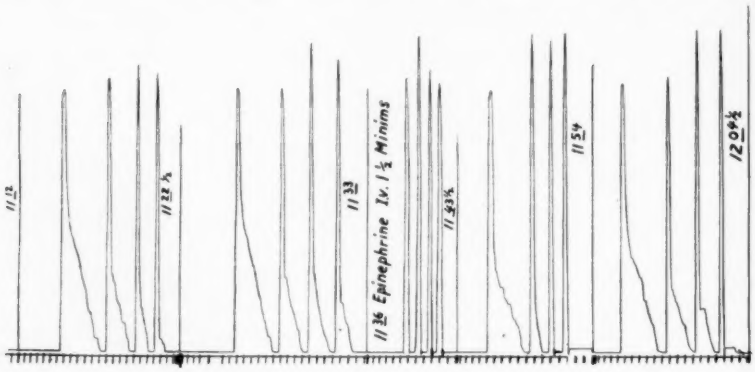


Fig. 7.—Effect of epinephrine hydrochloride on myotonia. Patient P; thumb movements; time expressed in seconds. After two control tests, 1½ minims (0.093 cc.) of epinephrine hydrochloride was given intravenously. The marked effect is evident in the next test.

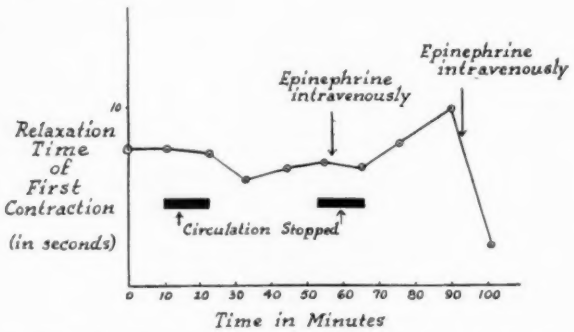


Fig. 8.—Peripheral nature of effect of epinephrine on myotonia. Patient P. The circulation to the thumb muscles was stopped by means of a blood pressure cuff around the arm from a minute and a half before the second test until after the third test. No effect on the myotonia is evident. The circulation was again stopped from just before the sixth test until after the seventh test. One and a half minims (0.093 cc.) of epinephrine hydrochloride was injected intravenously after the sixth test, but this could not reach the muscle and no effect was evident in the seventh test. Later, 1½ minims of epinephrine hydrochloride was again injected with the circulation intact, and a marked effect was evident.

11. Schweitzer, A., and Wright, S.: The Action of Adrenaline on the Knee Jerk, J. Physiol. **88**:476, 1937.

to the hand, an intravenous injection of epinephrine did not affect the test performed seven minutes later. A later injection with the circulation intact showed a marked effect. These experiments indicate that the effect of epinephrine is probably on the muscle or the neuromuscular junction.

Gruber [12] has shown that epinephrine can produce a marked increase in the extent of contraction of cats' muscles. This suggests the possibility that the effect of epinephrine on myotonia may be due to an increase in the strength of the extensor muscles. The extensor muscles were weak in all patients, and it was only with difficulty that patient P, for example, could raise a 150 Gm. weight in the ergograph with them. In this patient even the minor decreases in myotonia produced by epinephrine were greater than could be produced by adding 200 Gm. to the extending force. It would have to be postulated, then, that the strength of the extensor muscles was increased more than 100 per cent. Although obviously unlikely, this was shown by experiment not to occur.

Since the 6 patients who showed improvement with epinephrine represented all grades of severity of dystrophia myotonica, it seems reasonable to conclude that the experimental results are representative. These results are surprising in that they differ from those of other investigators of the effect of epinephrine. Pansini (cited by Poncher and Woodward [13]) found that epinephrine made the myotonia congenita of his patient definitely worse. Lindsley and Curnen,[14] estimating the degree of myotonia by the duration of the associated electrical activity, reported that 0.35 cc. of a 1:1,000 solution of epinephrine hydrochloride given intravenously to a patient with myotonia congenita caused a marked increase in the duration and size of the groups of nerve impulses. The same authors found no effect from epinephrine in a patient with dystrophia myotonica. Kennedy and Wolf,[15] dealing with cases of myotonia congenita and dystrophia myotonica, stated that epinephrine produced "extreme initial rigidity in myotonia."

The different experience of these other workers cannot be explained, but the method of investigation used with the patients in the present series is least open to criticism. The response of patients with dystrophia myotonica may be different from the response of patients with myotonia congenita. The possibility that adrenal insufficiency not present in myotonia congenita exists in dystrophia myotonica and that the effect of epinephrine is evident only in the presence of such a deficiency, and not under normal conditions, cannot be overlooked.

Insulin.—Three experiments were performed on patient P to determine the effect of insulin (fig. 9). In each experiment the decrease in myotonia was fairly marked and unequivocal. The greatest decrease occurred when the patient was showing definite hypoglycemic symptoms, such as nervousness, faintness and sweat-

12. Gruber, C. M.: Studies in Fatigue: XI. The Effect of Intravenous Injection of Massive Doses of Adrenalin upon Skeletal Muscle at Rest and Undergoing Fatigue, Am. J. Physiol. **61**:475, 1922.

13. Poncher, H. G., and Woodward, H.: Pathogenesis and Treatment of Myotonia Congenita, Am. J. Dis. Child. **52**:1065 (Nov.) 1936.

14. Lindsley, D. B., and Curnen, E. C.: An Electromyographic Study of Myotonia, Arch. Neurol. & Psychiat. **35**:253 (Feb.) 1936.

15. Kennedy, F., and Wolf, A.: Experiments with Quinine and Prostigmin in Treatment of Myotonia and Myasthenia, Arch. Neurol. & Psychiat. **37**:68 (Jan.) 1937.

ing. A direct correlation existed between the degree of these symptoms and the decrease of myotonia. When 25 Gm. of dextrose was given because of these hypoglycemic symptoms a marked increase in myotonia occurred. Since the decrease in myotonia was most marked at the time the body was pouring out epinephrine to counteract hypoglycemia, it seems most reasonable to assume that the decrease of myotonia was due to mobilization of epinephrine.

Quinine.—Results with the intravenous injection of quinine dihydrochloride in patients P and M are shown in table 4 and figure 10. The effect was obvious in a few minutes and still marked after eighty minutes. Complete abolition of myotonia was not obtained. In patient P more complete abolition of the myotonia could be obtained, for a short time, by the subcutaneous injection of epinephrine than by the intravenous injection of 10 grains (0.65 Gm.) of quinine dihydrochloride. The

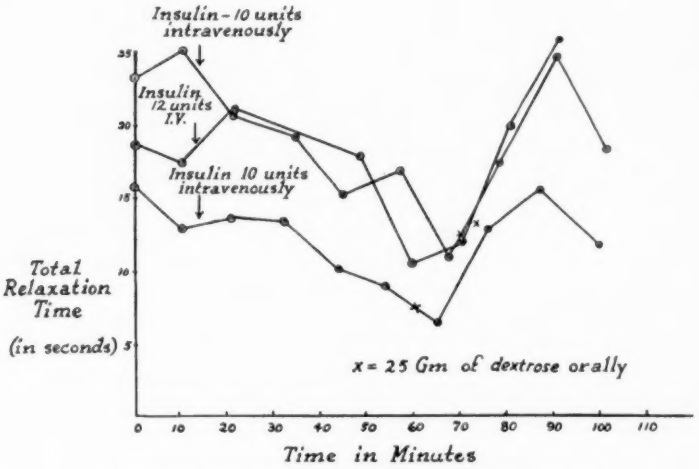


Fig. 9.—Effect of insulin on myotonia. Patient M.

oral administration of quinine also produced a marked decrease of the myotonia. Doses of more than 5 grains (0.325 Gm.) three or four times a day were not well tolerated by either patient P or M, and with this dose an appreciable residue of myotonia was still present. The graphic method of determining the results was less valuable for following the effect of administration of quinine by mouth, because of the duration of the experiments and the necessity for putting the patient in the apparatus several times during the day (see "Method of Investigation"). Some idea of the effect of the oral administration of 10 grains of quinine dihydrochloride on patient P is obtained, however, from the following: Ten grains of quinine dihydrochloride was given orally at 10: 38 a. m., at which time the total relaxation time was 17½ seconds; at 11: 33 a. m. the total relaxation time was 15½ seconds; at 12: 16 p. m., just before taking the patient from the machine, it was 11¼ seconds. After lunch, at 1: 43 p. m., the total relaxation time was 10 seconds; at 2: 05 p. m. it was 7¾ seconds. After supper, at 5: 38 p. m., it was 15¾ seconds.

TABLE 4.—*Total Relaxation Times After Injection of Quinine Dihydrochloride, Calcium Gluconate and Ephedrine Sulfate*

Experiment No.	Patient	Control Period: Total Relaxation Time (Sec.) at Successive 10 Min. Intervals			Drug Administered	Total Relaxation Time (TRT), in Seconds, and Interval (M), in Minutes, After Injection of Drug													
						TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M
36	P	18¾	14½	16¼	Quinine dihydrochloride, 10 gr. (0.65 Gm.) intravenously	9¼	6	8	16	6¼	27	7½	37	6¼	48	6½	58	7	69
39	P	16	18¾	15	Quinine dihydrochloride, 10 gr. intravenously	8	5	4	15	4	25	4¼	36	4¾	46	3	57	4¼	78
65	M	48¼	47¾	39	Quinine dihydrochloride, 10 gr. intravenously	13½	6	3½	16	3¼	25								
67	M	54	45½	53¾	Quinine dihydrochloride, 5 gr. (0.325 Gm.) intravenously	23	7	29	18	15	29	13¼	39	7½	50	6¾	72	25¼	83
41	P	....	12¾	10½	Calcium gluconate, 15 gr. (0.975 Gm.) intravenously	10¼	3	8	13	7¾	24	8½	34	9¾	45	10¾	55	10¾	66
45	M	24¼	33	27	Calcium gluconate, 15 gr. intravenously	14	5	17¼	16	16¼	30	14¾	44	17	55	13	67	18¼	78
60	B	....	11¼	11	Calcium gluconate, 15 gr. intravenously	7	7	4¾	17	6½	28	2¾	39	7	50				
68	B	14	13¼	14½	Calcium gluconate, 30 gr. (1.95 Gm.) intravenously	7	4	3½	15	4	26	5	38	10¼	49	11½	50		
7	P	11½	10¾	11½	Ephedrine sulfate, ¾ gr. (0.045 Gm.) subcutaneously	12	6	11½	16	12¾	27	11¼	37	12¼	48	10½	58	10¾	69
28	M	23	24	25½	Ephedrine sulfate, ½ gr. (0.0375 Gm.) subcutaneously	21	6	21	17	23¼	28	24¾	39	24¼	50	22¾	61	25½	72
46	..	8¼	11	8¼	Ephedrine sulfate, ⅜ gr. (0.025 Gm.) intravenously	8¼	5	7½	16	7¼	26	8	37	8¼	47	6	58	5¼	68

The effect of quinine on myotonia was discovered by Wolf [16] in 1936 and has since been confirmed by many workers.[17]

Quinidine Sulfate.—This drug was given to patients P and M and produced definite diminution of myotonia in both. It was given by mouth only, and the observations were not accurate and detailed enough to make possible any comparison of the effectiveness of quinidine and quinine. In one experiment, 10 grains (0.65 Gm.) of quinidine sulfate was given orally to patient P at 8:48 a. m., at which time the relaxation time was 27¼ seconds; at 10:07 a. m., the total relaxation time was 7½ seconds, and at 10:59 a. m. it was 8¾ seconds.

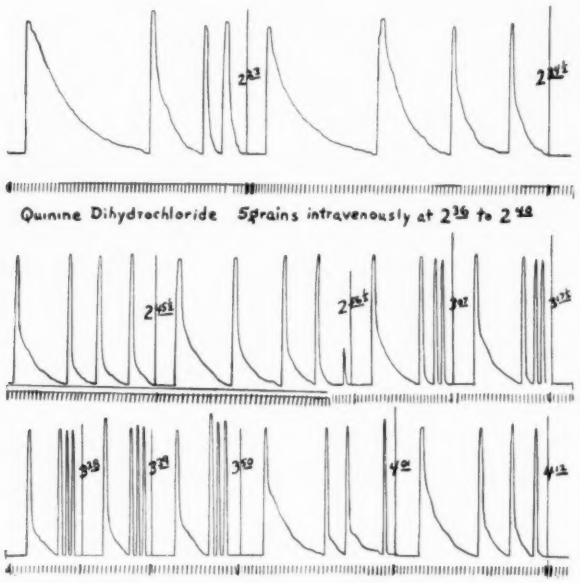


Fig. 10.—Effect of quinine on myotonia. Patient M; thumb movements; time expressed in seconds.

After two control tests (upper row), 5 grains (0.325 Gm.) of quinine dihydrochloride was given intravenously. The second and third rows of curves show the effect of the quinine as shown by tests taken at approximately ten minute intervals.

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16. Wolf, A.: Quinine: An Effective Form of Treatment for Myotonia; Preliminary Report of Four Cases, Arch. Neurol. & Psychiat. **36**:382 (Aug.) 1936.

17. (*a*) Kennedy, F., and Wolf, A.: Quinine in Myotonia and Prostigmine in Myasthenia: A Clinical Evaluation, J. A. M. A. **110**:198 (Jan. 15) 1938. (*b*) Smith, W. A.: Quinine Treatment of Myotonia Congenita, ibid. **108**:43 (Jan. 2) 1937. (*c*) Kolb, L. C.; Harvey, A. M., and Whitehill, M. R.: A Clinical Study of Myotonic Dystrophy and Myotonia Congenita with Special Reference to the Therapeutic Effect of Quinine, Bull. Johns Hopkins Hosp. **62**:188, 1938. (*d*) Buchstein, H. F.: Myotonic Dystrophy (Myotonia Atrophica): Report of Case, Proc. Staff Meet., Mayo Clin. **13**:366, 1938. (*e*) Hawke, W. A.: Myotonia Congenita: Report of a Case Treated by Quinine, J. Pediat. **13**:236, 1938. (*f*) Holland, G., and Feld, W.: Zur Beeinflussungsmöglichkeit der Myotonia congenita durch Chinin, Deutsche med. Wchnschr. **64**:566, 1938.

Calcium.—Calcium gluconate, given intravenously to patients P, M and B (figs. 11 and 12), produced definite improvement in each (table 4). The improvement varied in the different patients, but was most marked in patient B. It is interesting that this patient had a low normal calcium content of the blood and an unequivocal Chvostek sign. In patient B the effect was evident 4 minutes after the injection and was at its height in 26 to 39 minutes. An interesting phenomenon noted in this patient was the difficulty in completing the contraction, which was most evident at the height of the calcium effect and at the time when the myotonia

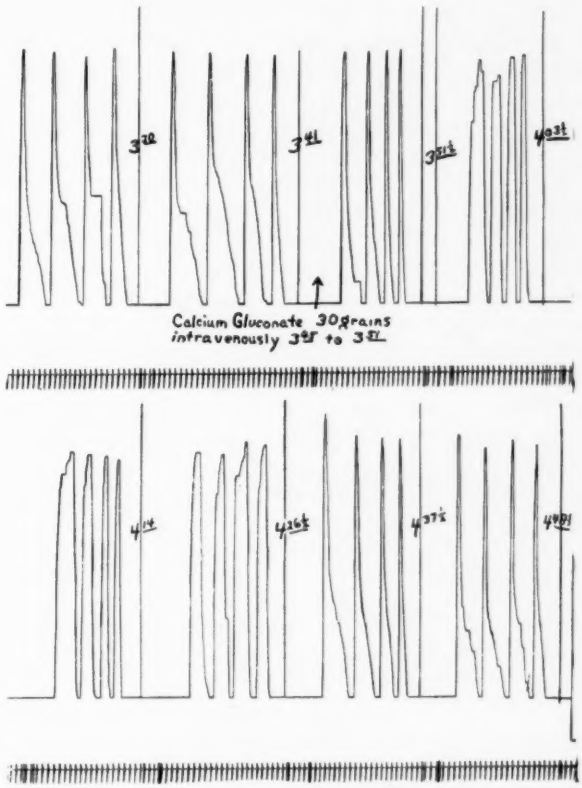


Fig. 11.—Effect of calcium on myotonia. Patient B; thumb movements; time expressed in seconds.

Note the increasing difficulty with contraction as the myotonia decreases.

was least marked (fig. 11). At this time the patient was able to carry out the contraction with normal rapidity for most of its extent, but difficulty was experienced in completing the contraction. To the patient it seemed as though the rider of the ergograph were stuck. This difficulty in contraction was more evident after 30 grains (1.95 Gm.) of calcium gluconate than after 15 grains (0.975 Gm.), and its degree varied inversely with the degree of myotonia; as the myotonia returned the difficulty in contraction disappeared. A somewhat similar phenomenon was observed under the influence of cold (see page 656).

Lindsley and Curnen [14] also found that intravenous injection of calcium decreased myotonia. Abrahamson [18] observed improvement of myotonia by the oral use of thyroid and calcium, and Pamboukis [19] reported temporary relief by the oral use of calcium chloride and acetylsalicylic acid.

Ephedrine.—In patient P no effect from ephedrine sulfate was observed within seventy minutes, even when given intravenously (table 4). Comroe [20] reported improvement in a patient with myotonia congenita with the use of ephedrine sulfate by mouth.

Prostigmine.—In 4 experiments with prostigmine (table 5) no definite effect was present. Since the experiments were brief and the doses of prostigmine not large, no definite conclusions can be drawn. Russell and Stedman; [21] Kennedy and Wolf,[22] and Kolb, Harvey and Whitehill [17c] found that prostigmine aggravated myotonia.

Pilocarpine.—In 3 experiments on patient P (table 5), pilocarpine hydrochloride failed to produce an appreciable change in the myotonia in spite of the marked reactions (flushing, salivation and abdominal cramps). Monrad-Krohn [23] found that 0.0075 Gm. of pilocarpine hydrochloride given intravenously caused a marked diminution of myotonia. Pamboukis [19] and Lindsley and Curnen [14] reported that pilocarpine produced an increase in myotonia in their patients.

Acetylcholine and Acetylbetamethylcholine.—One experiment with acetylcholine hydrobromide (table 6; experiment 58) and 4 with mecholyl (acetylbetamethylcholine) (table 5), given subcutaneously, were performed. No definite effect on the myotonia was evident, although general reactions were marked. A decided muscular effect following subcutaneous injection would be unlikely because of the rapid destruction of the drug. The effects of acetylcholine have been divided into the muscarine-like and the nicotine-like action. It is the nicotine-like action which is responsible for the effect of acetylcholine on skeletal muscle.[24] Mecholyl has practically no nicotine-like action and might not be expected to produce an effect on myotonia unless it did so as a result of its muscarine-like action.[25] Lanari [26] found that the intra-arterial injection of 0.04 Gm. of acetylcholine hydrobromide,

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18. Abrahamson, I.: Myotonia Accusata, J. Nerv. & Ment. Dis. **52**:144, 1920.

19. Pamboukis, G.: Bemerkungen über einige myotonische Züstande, Schweiz. Arch. f. Neurol. u. Psychiat. **26**:84, 1930.

20. Comroe, B. I.: Thomsen's Disease (Myotonia Congenita), Am. J. M. Sc. **189**:714, 1935.

21. Russell, W. R., and Stedman, E.: Observations on Myotonia, Lancet **2**:742, 1936.

22. Kennedy and Wolf, footnotes 15 and 17a.

23. Monrad-Krohn, G. H.: A Case of Myotonia with a Striking Reaction to Pilocarpin, Acta psychiat. et neurol. **5**:241, 1930.

24. Dale, H. H., and Gasser, H. S.: The Pharmacology of Denervated Mammalian Muscle: I. The Nature of the Substances Producing Contracture, J. Pharmacol. & Exper. Therap. **29**:53, 1926.

25. Bacq, Z. M., and Brown, G. L.: Pharmacological Experiments on Mammalian Voluntary Muscle, in Relation to the Theory of Chemical Transmission, J. Physiol. **89**:45, 1937.

26. Lanari, A.: Acción contracturante de la acetilcolina en la musculatura estriada de enfermos miotónicos, Rev. Soc. argent. de biol. **12**:207, 1936.

TABLE 5.—*Total Relaxation Times After Injection of Prostigmine, Pilocarpine and Mecholyl*

Experiment No.	Patient	Control Period: Total Relaxation Time (Sec.) at Successive 10 Min. Intervals			Drug Administered	Total Relaxation Time (TRT), in Seconds, and Interval (M), in Minutes, After Injection of Drug											
						TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M
13	P	10¼	9½	10	Prostigmine, 0.50 mg. subcutaneously	10¼	6	9¾	16	9¾	27	11½	37	10¾	48	10¼	58	10¼	69
14	P	10¼	11¾	9½	Prostigmine, 1.25 mg. subcutaneously	8½	5	10¾	47	12	57	10½	68						
15	P	9	7½	6¾	Prostigmine, 1.5 mg. subcutaneously	7	5	7½	17	7¾	27	5¾	38	7¾	48	10½	59		
31	M	25¾	31½	30¼	Prostigmine, 1 mg. subcutaneously..	27¼	6	25½	18	21	27	19¼	40	21¼	51	25	62		
1	P	15½	15¼	17	Pilocarpine, 1/20 gr. (0.0032 Gm.) subcutaneously	15½	3	14¼	13	16½	24								
3	P	16½	16	16	Pilocarpine, 1/10 gr. (0.0064 Gm.) subcutaneously	14¾	5	15	15	12	26	14	36	13	47	12¾	57		
4	P	11¾	12	13	Pilocarpine, 3/20 gr. (0.0098 Gm.) hypodermically	10	5	11¾	15	11½	26	14	37	12¾	47	14	57		
11	P	8¾	9¼	8¼	Mecholyl, 20 mg. subcutaneously.....	9¼	5	9¾	15	8	26	8¾	37	7½	47	9	58	8¼	68
12	P	9¼	9½	9	Mecholyl, 35 mg. subcutaneously.....	8¾	5	8¼	16	9¾	26	9	37	9½	47	9¼	58	8¼	68
21	P	16	12¾	13¼	Mecholyl, 40 mg. subcutaneously.....	10¾	6	10¾	17	12½	27	13¼	37	11½	48	12¼	58		
27	M	27½	27½	29	Mecholyl, 25 mg. subcutaneously.....	25½	6	30½	17	35¼	28	30¼	39	28½	50				

which in normal persons produces no motor effect, provoked in myotonic patients a reversible muscular contracture in the extremity into which it was injected, but after the immediate effects had passed the patients did not observe any change in the myotonia.

Atropine.—Only one experiment with atropine was performed (table 6; experiment 59). No definite effect was evident following the intravenous injection of 1/100 grain (0.6 mg.) of atropine sulfate. Erb,[2] Bremer [8] and Keschner and Finesilver [27] stated that atropine had no evident effect on myotonia. Weiss and Kennedy [28] and Pamboukis [19] observed improvement in myotonia following administration of atropine.

Benzedrine.—In patient P the oral administration of 40 mg. of benzedrine sulfate produced no definite effect on the myotonia in seventy minutes (table 6; experiment 22).

Ergotamine.—In patient P 1 mg. of ergotamine tartrate given subcutaneously did not produce an appreciable effect in fifty minutes (table 6; experiment 40). Lindsley and Curnen [14] reported that ergotamine tartrate (0.25 mg., intravenously) did not affect the duration of the myotonia.

Alcohol.—In 1 experiment performed on patient P (table 6; experiment 19) no effect on myotonia was observed after 3 ounces (85 cc.) of whisky. Improvement following the ingestion of alcohol has been reported by many authors. It was observed by Blumenau (cited by Erb [2]) and by Erb,[2] and was recently reported again by Russell and Stedman [21] and Kennedy and Wolf.[17a] Since the patient showed no other effect, it is probable that his capacity had been misjudged (table 6; experiment 19).

Scopolamine.—Patient M showed such a marked general reaction after the subcutaneous injection of 1/120 grain (0.5 mg.) of scopolamine hydrobromide that the experiment had to be discontinued after forty minutes. No definite effect on the myotonia was evident. Patient P showed no effect in 35 minutes (table 6; experiments 53 and 54). Bremer [8] found that scopolamine did not affect the myotonia in his case.

Caffeine.—The intravenous administration of 3½ and 7½ grains (0.2275 and 0.4875 Gm.) of caffeine with sodium benzoate did not affect the myotonia in patient P (table 6; experiments 48 and 49).

COMMENT

As knowledge of myotonia and of contractures increases, a striking similarity in properties becomes evident. It is true that the term "contracture," used even in its strict physiologic sense, includes an apparently heterogeneous group of phenomena. The term as defined by Gasser [29] includes sustained contractions of muscles which are distinguished from tetanic contractions by the absence of oscillatory electrical variations

27. Keschner, M., and Finesilver, B.: Myotonia Atrophica (Dystrophia Myotonica), J. Neurol. & Psychopath. **5**:341, 1925.

28. Weiss, S., and Kennedy, F.: Clinical Experiments in Myotonia Congenita (Thomsen) with Especial Reference to the Parasympathetic Nervous System, Arch. Neurol. & Psychiat. **11**:543 (May) 1924.

29. Gasser, H. S.: Contractures of Skeletal Muscle, Physiol. Rev. **10**:35, 1930.

TABLE 6.—*Total Relaxation Times After Injection of Various Drugs*

Experiment No.	Patient	Control Period: Total Relaxation Time (Sec.) at Successive 10 Min. Intervals			Drug Administered	Total Relaxation Time (TRT), in Seconds, and Interval (M), in Minutes, After Injection of Drug													
						TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M	TRT	M
58	B	9½	10¼	10¼	Acetylcholine hydrobromide, 0.1 Gm. subcutaneously	9¾	9	11¼	20	10¼	30								
59	B	....	11¾	11¾	Atropine sulfate, 1/100 gr. (0.6 mg.) intravenously	13¼	5	12	16	9	28	13½	38	13¾	52				
22	P	11½	10½	10¾	Benzedrine sulfate, 40 mg. orally	8½	6	9	17	7¾	28	8¾	38	9	49	8¼	59	8½	70
40	P	....	9½	9	Ergotamine tartrate, 1 mg. subcutaneously	9½	9	8¼	19	8¼	30	9½	41	9	51				
19	P	....	15¼	13½	Whisky, 3 oz. (85 cc.) orally	14¾	6	13¼	16	13	27	12¾	37	12½	48	12½	59	12½	69
53	M	62	59½	63	Scopolamine hydrobromide, 1/120 gr. (0.5 mg.) subcutaneously	72½	4	52	17	61	29	48¼	41						
54	P	14	10½	11¾	Scopolamine hydrobromide, 1/200 gr. (0.3 mg.) subcutaneously	10¾	3	12¾	14	15¼	24	13¾	35						
48	P	....	12½	12	Caffeine with sodium benzoate, 3½ gr. (0.228 Gm.) intravenously	10¼	5	11¼	16	10	27	11	38	10¼	48				
49	P	11½	14½	10¾	Caffeine with sodium benzoate, 7 gr. (0.455 Gm.) intravenously	13¼	1	13½	11	13	23	13¼	34	11½	45				

(action currents) and by the absence of propagation of the contraction through the muscle fiber. It is typical, in a sense, of the present status of the subject of contractures that the two main criteria set up for their recognition should have been challenged in the case of what is considered a typical contracture, veratrine contracture. Action currents [30] and propagation of the contraction [31] are said to occur in veratrine contracture. Action currents are thought to occur also in other contractures. In spite of this confusion concerning the nature of contractures and the criteria for recognition of contractures, the existence of a type of sustained contraction which differs from tetanus is unquestioned. Examination of Tiegel's contracture, veratrine contracture, neuromuscular contracture and acetylcholine contracture reveals similarities which justify grouping them together and separating them from tetanic contractions. It is proposed to point out these similarities so far as they are also seen in myotonia. A brief description of these contractures is first essential.

When a very irritable muscle is stimulated with successive supramaximal break induction shocks so as to give a series of twitches, it often happens that during the first contractions the relaxation is incomplete. The level of the bases of the separate twitches progressively rises, but a maximum is soon reached and succeeded by a fall.[29]

The relaxation is incomplete because of persistence of the contraction which has been called Tiegel's contracture. Tiegel's contracture occasionally occurs after a single stimulation of a muscle especially susceptible to its production. It is then seen as persistence of the contraction following the twitch. Different muscles show this contracture in varying degrees. The contracture occurs and is gone before the muscle is fatigued, and must be distinguished from the "fatigue contracture," which occurs as the muscle tires.

Certain drugs, most typical of which is veratrine, predispose a muscle to the production of contractures following stimulation; thus, the effect of veratrine is not evident until the muscle is stimulated, but once the muscle is stimulated a normal rapid twitch is followed by a prolonged contracture. Gasser [29] expressed the belief that veratrine and a number of other substances having a similar action merely reveal "a fundamental characteristic of skeletal muscle." That this characteristic may be the same as that exhibited as Tiegel's contracture on direct electrical stimulation seems probable. Kruse [32] observed, for example,

30. (*a*) Hoffmann, P.: Ueber die Aktionsströme des mit Veratrin vergifteten Muskels, Ztschr. f. Biol. **58**:55, 1912. (*b*) Harvey, A. M.: The Actions of Quinine on Skeletal Muscle, J. Physiol. **95**:45, 1939.

31. Feng, T. P.: The Propagation of Contractures of the Veratrine Type, Chinese J. Physiol. **10**:535, 1936.

32. Kruse, T. K.: The Influence of Veratrine and Epinephrine on Skeletal Muscle, J. Pharmacol. & Exper. Therap. **19**:266, 1922.

that the same type of prolonged contraction obtained by a strong stimulus could be produced by a stimulus of moderate intensity following veratrine.

Tiegel's contracture has also been shown to be present in man by Mosso [33] and by Schäffer.[34] On direct stimulation of the flexor muscles in the forearm by strong galvanic or faradic currents at two second intervals, the slowness of relaxation becomes evident in a few contrac-

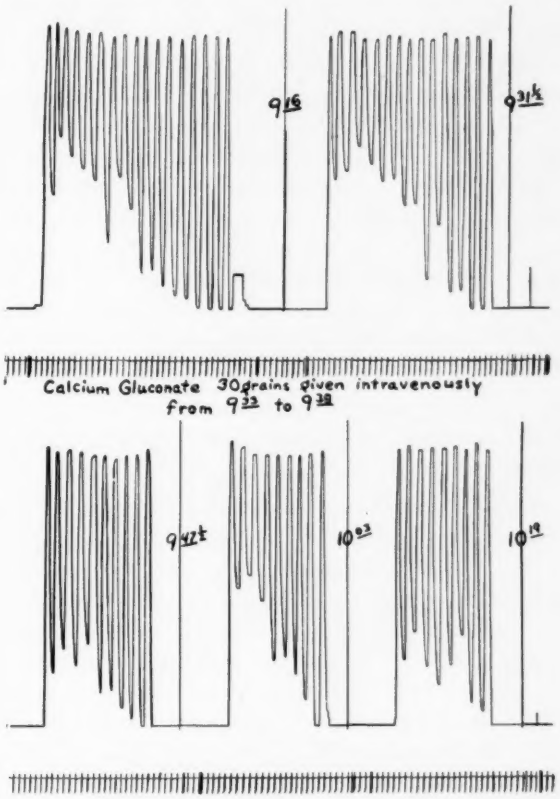


Fig. 12.—Effect of calcium on myotonia. Patient B; time expressed in seconds. This is the type of curve obtained when the patient contracts his thumb every two seconds even when relaxation is not entirely completed.

tions, reaches a maximum after several contractions and then gradually disappears. Some of the curves obtained by Schäffer are almost exact

33. Mosso, A.: Ueber die Gesetze der Ermüdung. Untersuchungen an Muskeln des Menschen, Arch. f. Physiol., 1890, p. 89.

34. Schäffer, H.: Beiträge zur Frage der autonomen Innervation des Skelettmuskels. Ueber die Tiegelsche Contraktur beim Menschen, Arch. f. d. ges. Physiol. **185**:42, 1921.

replicas of those in figure 12. Mosso also observed this slowness of relaxation, but to a less degree, after indirect stimulation and in slight degree after very powerful voluntary contractions. Schäffer found that persons varied markedly in the degree to which they showed this contracture and suggested the possibility that those who showed it in a high degree bordered on the pathologic. Since the contracture occurs even when the brachial plexus is blocked by procaine, reflex production is excluded.

Most attempts to produce contractures by stimulation of the nerve have been unsuccessful. Beritoff [35] occasionally observed it in certain susceptible frogs after a single shock to the nerve. Bremer [36] has shown, however, that a contracture can be produced regularly in susceptible frogs' muscles by suitably spaced electrical stimuli to the nerve. Curves of such "neuromuscular" contractures resemble those produced by direct stimulation of the muscle. Neuromuscular contracture is most easily produced in those muscles which tend to react with a Tiegel's contracture.

Acetylcholine in adequate concentration produces a contracture in many of the muscles of a frog, but not in normal mammalian muscles. If the nerve to the muscle is permitted to degenerate, however, mammalian muscle shows a response to acetylcholine similar to that of frog's muscle. Wachholder [37] has shown that those amphibian muscles which show the greatest sensitivity to acetylcholine exhibit the most marked Tiegel contractures. A similarity of reaction has been shown between acetylcholine contractures and veratrine contractures.[38] It seems probable that the same fundamental tendency to contracture response is involved in these instances. In view of the minute quantities required for the production of a contracture, acetylcholine appears to furnish an exceptionally adequate stimulus for the elicitation of this response.

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35. Beritoff, I. S.: Ueber die Contractur und den Tetanus der quergestreiften Muskeln, Arch. f. d. ges. Physiol. **198**:590, 1923.

36. Bremer, F.: (*a*) Pharmacologie de la contracture neuromusculaire des amphibiens, Compt. rend. Soc. de biol. **98**:607, 1928; (*b*) Signification physiopathologique de la contracture neuro-musculaire des amphibiens. Son homologie avec la rigidité myotonique de la pathologie humaine, ibid. **100**:205, 1929; (*c*) Researches on the Contracture of Skeletal Muscle, J. Physiol. **76**:65, 1932.

37. Wachholder, K.: Untersuchungen über "tonische" und "nicht tonische" Wirbeltiermuskeln: II. Acetylcholin- und Tiegelsche Contractur in ihren Beziehungen zueinander und zur tetanischen Kontraktionsform. Die Plastizität der bieden Muskelarten, Arch. f. d. ges. Physiol. **226**:255, 1930.

38. Riesser, O., and Neuschlosz, S. M.: II. Ueber die durch Nikotin und Kaliumsalze ausgelöste Erregungskontraktur des Froschmuskels und über die rezeptive Substanz Langleys, Arch. f. exper. Path. u. Pharmakol. **92**:254, 1922.

From the preceding it may be concluded that a tendency to contracture exists in the muscle. This "contracture reaction tendency" varies in different muscles of the same animal. It is augmented by certain drugs, notably veratrine, and by denervation. It may be brought out by electrical stimulation of the muscle (Tiegel's contracture), by electrical stimulation of the nerve (neuromuscular contracture) or by acetylcholine. Bremer [36c] expressed the belief that this "aptitude for contracture" characterizes a "primitive evolutionary state of the muscle fibers which has been passed by some fibers and not by others. . ."

The quantitative similarity in the energy metabolisms of contractions and of contractures (veratrine, caffeine and Tiegel's) indicates that the contracture is an active state rather than a slowing of the process of relaxation and is evidence against the participation of a special contractile apparatus, as advocated, for example, in Botazzi's sarcoplasmic hypothesis (see Bremer [36c] for references).

In comparing the characteristics of myotonia with those of the contractures described, it is evident that myotonia following voluntary contraction is comparable with the neuromuscular contracture. Their identity has been advocated by Bremer.[36b, c] Myotonia following electrical stimulation is comparable with Tiegel's contracture, especially as described in man by Mosso [33] and by Schäffer.[34] This similarity of the myotonic reaction and Tiegel's contracture in man, pointed out by Schäffer,[39] is so marked that it is difficult to avoid the conclusion that they are different degrees of the same phenomenon.

Possibly the most striking similarity is what has been called the "fatigability" of the contractures; that is, in a succession of contractions, the contracture decreases and soon disappears. After a rest the contracture can again be obtained. The "fatigue" of the contracture, however, occurs long before the muscle fatigues. This interesting "fatigability" is a common property of Tiegel's contracture in frogs,[29] Tiegel's contracture in man,[34] veratrine contracture [29] and neuromuscular contracture.[36c] Its occurrence in myotonia has already been described in detail. It is not evident in acetylcholine contractures. This property of "fatigability" suggests that some change occurs in the muscle after each reaction by contracture which decreases the tendency of the muscle to react by contracture. It is possible that acetylcholine is such an adequate stimulus for the production of contracture that the muscle fatigues before the stimulus becomes ineffective, whereas less adequate stimuli (electrical) soon cease to be effective in producing this response. This explanation receives some confirmation in Wachholder's [37] observa-

39. Schäffer, H.: Skelettmuskel und autonomes Nervensystem, nach Untersuchungen über die Tiegelsche Kontraktur am Menschen, Berl. klin. Wchnschr. **57**:728, 1920.

tion that in muscles especially susceptible to the production of Tiegel's contracture decrease in the degree of contracture does not occur until the muscle begins to fatigue.

Epinephrine inhibits Tiegel's contracture in man.[34] The marked effect of epinephrine on voluntary myotonia has already been noted. Epinephrine injected immediately before or simultaneously with acetylcholine inhibits or totally prevents the production of acetylcholine contracture in denervated mammalian muscle.[40] Although Dale and Gaddum [41] attributed this inhibition to a decrease of the capillary permeability which prevented acetylcholine from reaching the muscle, Brown [42] found that the twitch contraction produced by intraarterial injection of acetylcholine close to the muscle was not inhibited by epinephrine. That the forcing of acetylcholine into the arteries under considerable pressure might have overcome the decrease in permeability seems somewhat labored, and a direct action of the epinephrine on the muscle is still to be considered. In cases of Tiegel's contracture in man [34] and of myotonia, the action of epinephrine has been shown to be on the muscle. Epinephrine has not been shown to have any effect on veratrine contracture or neuromuscular contracture.[36c] It is possible, as Riesser and Neuschlosz [43] suggested, that some experimental condition necessary for the effect to become evident has been overlooked.

Quinine markedly decreases myotonia and also suppresses veratrine contracture,[30b] neuromuscular contracture [44] and acetylcholine contracture in denervated mammalian muscles.[30b] The action of quinine is discussed later in greater detail.

Atropine decreases the height of Tiegel's contracture,[45] neuromuscular contracture,[36a] acetylcholine contracture [46] and veratrine contracture.[38] The effect of atropine on myotonia has been slight in most

40. Gasser, H. S., and Dale, H. H.: The Pharmacology of Denervated Mammalian Muscle: II. Some Phenomena of Antagonism, and the Formation of Lactic Acid in Chemical Contracture, J. Pharmacol. & Exper. Therap. **28**:287, 1926.

41. Dale, H. H., and Gaddum, J. H.: Reactions of Denervated Voluntary Muscle, and Their Bearing on the Mode of Action of Parasympathetic and Related Nerves, J. Physiol. **70**:109, 1930.

42. Brown, G. L.: The Actions of Acetylcholine on Denervated Mammalian and Frog's Muscle, J. Physiol. **89**:438, 1937.

43. Riesser, O., and Neuschlosz, S. M.: I. Ueber die durch Azetylcholin bewirkte Erregungskontraktur des Froschmuskels und ihre antagonistische Beeinflussung durch Atropin, Novokain und Kurare, Arch. f. exper. Path. u. Pharmakol. **91**:342, 1921.

44. Bremer, F., and Moldaver, J.: La contracture neuro-musculaire de Rana temporaria et le mécanisme de la transmission neuro-musculaire, Compt. rend. Soc. de biol. **127**:352, 1938.

45. Schäffer.[34] Wachholder.[37]

46. Brown.[42] Riesser and Neuschlosz.[43]

cases, but in 1 instance [28] it markedly decreased the myotonia. The lack of effect usually observed may well be correlated with the large doses required to produce an effect in the case of most of the contractures. Tiegel's contracture in man [34] is more sensitive than myotonia to the action of drugs and is markedly decreased by atropine.

Gasser [29] stated that "substances like calcium having a general action on the plasma membrane are generally antagonistic" to contractures. Calcium decreases veratrine contracture,[47] acetylcholine contracture [48] and myotonia.

Physostigmine increases acetylcholine contracture,[42] facilitates the production of neuromuscular contracture [49] and increases Tiegel's contractures in man.[34] Prostigmine, chemically related to physostigmine and having a similar action, has been shown to aggravate myotonia.

Alcohol decreases myotonia (see previous section) and inhibits veratrine contracture (von Frey, cited by Schüller and Athmer [50]).

Cold decreases veratrine contracture,[47] acetylcholine contracture [49] and the neuromuscular (physostigmine) contracture of Feng and Shen,[49] but increases the neuromuscular contracture of Bremer.[36c] It seems probable that various parts of the neuromuscular apparatus react differently to changes in temperature and that the final effect will vary in different cases. This may be the explanation of the anomalous results obtained on the effect of cold on myotonia.

Lanari,[26] using intra-arterial injection into the brachial artery, found that the injection in myotonic persons of an amount of acetylcholine which produced no effect in normal persons produced a slow contraction of the muscles of the forearm. These results, suggesting an increased sensitivity to acetylcholine and an increased tendency to contracture reaction such as is seen after denervation, furnish additional evidence that myotonia may be a contracture.

It is evident that the properties of myotonia are largely those of the group of contractures which have been described. If it is concluded that myotonia is a contracture, it follows that the location of the defect in myotonia is in the muscles. Several investigators have shown that the defect in myotonia is peripheral rather than central. Grund [51] found that the myotonic reaction persisted in limbs paralyzed by intra-

47. Lamm, G.: Untersuchungen über die Wirkung des Veratrins auf den quergestreiften Muskel: II. Mitteilung, Ztschr. f. Biol. **58**:37, 1921.

48. Riesser and Neuschlosz.[43] Gasser.[29]

49. Feng, T. P., and Shen, S. C.: Studies on the Neuro-Muscular Junction: II. The Contracture in Eserinized Muscle Produced by Nerve Stimulation, Chinese J. Physiol. **11**:51, 1937.

50. Schüller, J., and Athmer, F.: Ueber den Antagonismus der Lokalanasthetika gegenüber dem Veratrineffekt am Muskel, Arch. f. exper. Path. u. Pharmakol. **91**:125, 1921.

(Footnotes continued on next page)

thecal injection of stovaine (the hydrochloride of benzyldimethylaminomethylpropanol), so that all spontaneous and reflex activity was absent. Schäffer [52] showed that myotonia persisted when the nerve endings in the muscles were paralyzed by regional anesthesia. Kennedy and Wolf [15] found that mechanical and electrical myotonia persisted after spinal anesthesia and that the effect of quinine in inhibiting myotonia was present after spinal anesthesia.

Additional evidence that the defect is in the muscle can be obtained by analyzing that characteristic of myotonia already described as the "dual nature of the myotonic contracture." Since the duration of the myotonia is not affected by the duration of an associated tetanic contraction, the stimuli which maintain tetanic contraction must not affect the myotonia. Myotonia sets in only when the muscle contracts and not during maintenance of the contraction; the nerve impulses produce myotonia when they cause contraction of the muscle but not when they maintain contraction. Only when the patient relaxes the muscle and again contracts it, that is, when the mechanical change of contraction occurs, is another increment of myotonia added. The manifestation of myotonia is apparently more dependent on the changes associated with the actual contraction of the muscle than on the nature of the stimulus producing the contraction. This property of the myotonic muscle appears to be related to the necessity of a twitch for the manifestation of the veratrine contracture and accords well with the fact that myotonia is evident after contractions produced by diverse agents.

Some insight into the status of neuromuscular transmission can also be obtained from analysis of the dual nature of the myotonic contraction. If myotonia is assumed to result entirely from a defect in neuromuscular transmission which produces prolonged stimulation of the muscle, the independence of tetanic contractions which myotonia shows cannot be explained. In terms of the chemical hypothesis of neuromuscular transmission in skeletal muscle, prolonged stimulation would produce a repetitive response of the muscle if the acetylcholine liberated by the nerve impulse persisted long enough to stimulate the muscle fiber again after it had passed through the refractory phase. Such a prolonged action of acetylcholine could result from an increase in the amount of acetylcholine liberated by the nerve impulse or from a

51. Grund, G.: Ueber myokymische Kontraktur, Deutsche Ztschr. f. Nervenh. **64**:102, 1919; cited by Adie, W. J., and Greenfield, J. G.: Dystrophia Myotonica (Myotonia Atrophica), Brain **46**:73, 1923.

52. Schäffer, H.: Zur Analyse der myotonischen Bewegungsstörung, nebst Bemerkungen über die Tonusfunktion des Skelettmuskels, Deutsche Ztschr. f. Nervenh. **67**:225, 1920; cited by Adie, W. J., and Greenfield, J. G.: Dystrophia Myotonica (Myotonia Atrophica), Brain **46**:73, 1923.

decrease in the cholinesterase at the end plate or from both factors. Under such conditions, however, the longer the tetanic contraction, the longer would be the liberation of acetylcholine and the more marked the myotonia. The duration and course of myotonia would not be independent of the tetanic contraction. For similar reasons, it appears unlikely that a neuromuscular abnormality of the type previously described is present in addition to a muscular defect. From the observation that the myotonia is unaffected during the maintenance of tetanic contraction, it follows that a neuromuscular defect would be manifested in the tetanic contraction rather than in the myotonia. Although more careful study is necessary, the tetanic contractions in experiments such as the one shown in figure 4 appear to be of normal character.

The existence of increased sensitivity of the muscle to acetylcholine is suggested by Lanari's observations on the effect of intravenously injected acetylcholine in patients with myotonia.[26] Increased sensitivity to acetylcholine, however, cannot in itself explain myotonia. Although to the sensitized muscle fiber a normal stimulus would be relatively excessive, the muscle fiber, according to the "all or nothing principle," should respond no differently than it would to a stimulus which was merely adequate. Increased sensitivity of the muscle fiber to acetylcholine is of importance only when considered in association with the abnormal tendency of the muscle fiber to respond with myotonia.

Because of the contrast which myotonia shows to myasthenia, both in clinical features and in the responses to various drugs, Harvey[53] expressed the belief that myotonia was due to an abnormality of neuromuscular transmission, "the threshold of the end plates being lower, or the transmitter of excitation from the nerve endings being more slowly destroyed, than in the normal muscle." The following evidence is given in support of this hypothesis: (1) Quinine, which has a curare-like action in decreasing the excitability of the end plates,[30b] alleviates myotonia; (2) prostigmine, which inhibits cholinesterase and therefore the destruction of acetylcholine, aggravates myotonia; (3) potassium ions, which lower the threshold at the motor end plates, aggravate myotonia. Objections to the explanation of myotonia on the basis of increased sensitivity of the muscle fiber to acetylcholine or delayed destruction of acetylcholine have been given. Further analysis of the actions of the drugs, moreover, reveals that their actions may be interpreted in a different manner. Feng and Shen,[49] in studying the contracture in physostigminized muscle produced by nerve stimulation, concluded that in the production of the physostigmine contracture the sensitizing action of physostigmine on the muscle was probably as

53. Harvey, A. M.: The Mechanism of Action of Quinine in Myotonia and Myasthenia, J. A. M. A. **112**:1562 (April 22) 1939.

important as the protective effect of physostigmine on acetylcholine. They expressed the belief that the action of physostigmine on the muscle was to increase the sensitivity of muscle to acetylcholine, but it may equally as well have been to increase the tendency to contracture of the muscle. A similar action of prostigmine would account for its effect on myotonia. The importance of the curare-like action of quinine in overcoming myotonia must be questioned when it is recalled that epinephrine, which also alleviates myotonia, has a decurarizing action, similar to that of potassium ions.[54] The other actions of quinine on skeletal muscle appear to be more important in cases of myotonia. Quinine increases the refractory period of skeletal muscle and potentiates the response of skeletal muscle to single maximal induction shocks.[54] Especially noteworthy is the action of quinine by which it inhibits the contracture response of a denervated mammalian muscle to acetylcholine without significantly affecting the twitchlike response. It is highly significant that epinephrine also potentiates the response of skeletal muscle to direct stimulation[55] and inhibits the contracture response of denervated mammalian muscle.[40] Actions of drugs, it is evident, furnish no basis for assuming a neuromuscular defect in myotonia.

SUMMARY

The characteristics and reaction to drugs of voluntary myotonia have been studied in 10 patients with dystrophia myotonica. Numerous tracings of the contractions of the thumb were made by means of an ergograph. The fundamental characteristic was abnormal persistence of the state of contraction, which was evident as slowness of relaxation of the muscle. In every patient myotonia decreased in successive contractions until it was no longer evident, but returned with rest. Within limits the myotonia increased with increase in force of contraction.

The myotonic contractions appeared to be of dual nature, consisting of two superimposed components: one, a voluntary contraction of the usual type, starting and stopping as desired by the will; the other, a persisting contraction setting in at the time of the voluntary contraction and lasting for a definite time regardless of the duration of the voluntary component. The importance of this characteristic for the understanding of the nature of myotonia is discussed.

In some myotonic contractions slowness of the phase of contraction as well as of the phase of relaxation was recorded. On many occasions in a series of contractions the second and several succeeding contractions were weaker than the first contraction.

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54. Rosenblueth, A.; Lindsley, D. B., and Morison, R. S.: A Study of Some Decurarizing Substances, Am. J. Physiol. **115**:53, 1936.

55. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton and Company, 1929.

Neither venous congestion nor complete obstruction of the circulation appreciably influenced the myotonia. Cold unexpectedly decreased the myotonia in 1 patient.

A sensitive method was devised for determining the effect of drugs on voluntary myotonia. Epinephrine, which has usually been stated to increase myotonia, was shown definitely to decrease myotonia. The effect of epinephrine appears to be due to an action on the muscle itself rather than on the circulatory or the central nervous system. Quinine and quinidine markedly decreased myotonia. Calcium produced a definite, but less marked, decrease. Probably as a result of the mobilization of epinephrine, insulin decreased myotonia when symptoms of hypoglycemia were present. Many other drugs, including pilocarpine, ephedrine and mecholyl, did not influence myotonia.

On the basis of the similarities of the properties of myotonia to those of Tiegel's, veratrine, neuromuscular and acetylcholine contractures, it is suggested that myotonia is a contracture and that the defect in myotonia is chiefly or entirely in the muscle. Evidence is presented that a defect in neuromuscular transmission does not adequately explain the observed phenomena and is probably not present.

Drs. James J. Waring, E. H. Brunquist, R. W. Whitehead and R. S. Ravin made many helpful suggestions.

METRAZOL CONVULSIONS

CHANGES IN OXYGEN, CARBON DIOXIDE AND SUGAR CONTENTS OF ARTERIAL AND OF INTERNAL JUGULAR VENOUS BLOOD

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That there is obvious cerebral hypoxia during the metrazol convulsion, as indicated by a subnormal oxygen content of the arterial blood, has been demonstrated by Himwich and his associates.[1] Since only a single sample of blood from either an artery or the internal jugular vein was obtained during each convulsion, no further conclusions concerning the oxygen metabolism of the brain could be made.

The present study is concerned with changes in oxygen, carbon dioxide and sugar in blood from the basilic vein and particularly from the internal jugular vein and brachial artery obtained before, during the various stages of and after the metrazol convulsion. Passive and cooperative subjects with dementia praecox were utilized. The experiments were carried out in the morning, breakfast being withheld from all subjects. The gas determinations were made by the method of Van Slyke and the sugar determinations by the method of Folin and Wu.

RESULTS

Changes in Oxygen, Carbon Dioxide and Sugar Contents of Basilic Venous Blood.—Table 1 shows the changes in oxygen, carbon dioxide and sugar in the basilic venous blood taken before and at various intervals after the convulsion. In every case the following observations were made: 1. A diminished oxygen content was found within a minute after termination of the convulsion. 2. No consistent changes in carbon dioxide were evident until the stage of hyperpnea. 3. By this time the

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1. Himwich, H. E.; Bowman, K. M.; Fazekas, J. F., and Orenstein, L. O.: Effect of Metrazol Convulsions on Brain Metabolism, Proc. Soc. Exper. Biol. & Med. **37**:359-361 (Nov.) 1937.

oxygen had returned to a point higher than its original level. 4. A rise in sugar regularly occurred, reaching its maximum several minutes after the seizure.

TABLE 1.—*Changes in Oxygen, Carbon Dioxide and Sugar Contents of Basilic Venous Blood at Various Intervals After Metrazol Convulsion*

Case	Time (Minutes After Convulsion)	Blood Samples	Oxygen Content, Vol. %	Carbon Dioxide Content, Vol. %	Sugar, Mg. per 100 Cc.
1	Control	1	17.6	49.8	90
	2	2	11.0	49.0	135
2	Control	1	....	....	103
	½	2	....	....	111
	4	3	....	....	147
	11	4	....	....	189
	26	5	....	....	207
	42	6	....	....	244
3	Control	1	13.8	59.6	77
	1	2	2.5	45.6	106
	9	3	11.2	37.5	139
	21	4	8.6	40.9	128
	41	5	15.7	44.5	108
	55	6	16.8	47.9	80
	75	7	17.5	55.9	62
4	Control	1	9.2	52.0	89
	End of convulsion	2	7.8	53.6	92
	5	3	13.5	24.6	131
	15	4	9.1	28.5	111
	30	5	10.4	35.4	103
	45	6	11.7	41.4	97
	60	7	11.3	47.5	97
5	Control	1	10.7	53.2	89
	1	2	2.5	47.4	106
	14	3	12.6	27.8	124
	28	4	15.5	34.5	97
	38	5	16.2	38.2	94
6	Control	1	14.7	49.8	92
	1	2	5.6	51.0	106
	7	3	17.3	20.0	124
	15	4	14.8	25.8	118
	29	5	16.2	39.6	109
	60	6	14.4	49.8	94
7	Control	1	....	....	79
	1	2	....	....	79
	7	3	....	....	108
	22	4	....	....	89
	42	5	....	....	89
	62	6	....	....	91
8	Control	1	....	....	92
	1	2	....	....	114
	7	3	....	....	147
	13	4	....	....	173
	16	5	....	....	118
9	Control	1	....	....	79
	2	2	....	....	115
	9	3	....	....	128
	29	4	....	....	146
	60	5	....	....	118

Changes in Sugar in Arterial and in Internal Jugular Venous Blood.—Blood withdrawn from the internal jugular vein during and after the convulsion showed changes in sugar similar to those occurring in the blood from the basilic vein. In 1 case, although a marked fall in oxygen

occurred during the course of the convulsion, there was a variation of only 8 mg. of sugar per hundred cubic centimeters (table 2, case 17). In 3 instances, in which blood was withdrawn simultaneously from the internal jugular vein and the brachial artery before, during and after the convulsion, increases in sugar occurred in all the samples, so that there was little variation in the arteriovenous differences (table 3).

TABLE 2.—*Changes in Oxygen and Carbon Dioxide Contents of Brachial Arterial and Internal Jugular Venous Blood During the Various Stages of the Metrazol Convulsion, with Changes in Sugar Content of Internal Jugular Venous Blood in Three Cases*

		Brachial Artery			Internal Jugular Vein		
Case	Time	Oxygen Content, Vol. %	Carbon Dioxide Content, Vol. %	A — J*	Oxygen Content, Vol. %	Carbon Dioxide Content, Vol. %	Sugar, Mg. per 100 Cc.
10	Basal	20.3	43.8	7.7	12.6	52.0	60
	Beginning of convulsion	....	....	...	12.7	51.6	80
	2 min. after convulsion	20.1	22.0	3.1	17.0	37.9	77
	18 min. after convulsion	19.9	23.5	5.0	14.9	34.0	103
11	Basal	20.4	30.0	6.8	13.6	52.0	...
	Beginning of convulsion	....	....	...	13.4	54.0	...
	2 min. after convulsion	20.2	28.8	2.5	17.7	32.8	...
	16 min. after convulsion	20.9	24.3	7.2	13.7	51.6	...
12	Basal	19.9	30.3	6.4	13.5	50.4	...
	End of convulsion	....	....	...	6.9	57.1	...
	30 sec. after convulsion	19.7	29.8	9.0	8.7	31.9	...
	15 min. after convulsion	19.3	22.7	5.6	13.7	28.5	...
13	Basal	17.8	39.1	6.2	11.6	55.9	...
	1 min. after convulsion	16.0	46.4	1.9	14.1	49.1	...
14	Basal	22.5	....	...	....	....	...
	End of convulsion	16.9	....	...	....	....	...
15	Basal	....	....	...	14.1	60.0	97
	10 sec. after beginning of convulsion	....	....	...	11.0	60.0	102
	Middle of convulsion	....	....	...	12.3	63.2	111
	5 min. after convulsion	....	....	...	10.6	40.2	135
	10 min. after convulsion	....	....	...	10.4	41.8	141
16	Basal	....	....	...	14.1	50.2	...
	Beginning of convulsion	....	....	...	13.3	50.6	...
	1 min. after convulsion	....	....	...	17.9	29.3	...
17	Basal	....	....	...	13.4	54.2	128
	15 sec. after beginning of convulsion	....	....	...	11.4	56.0	130
	Middle of convulsion	....	....	...	9.8	59.2	128
	End of convulsion	....	....	...	7.2	60.0	120

* Difference in oxygen content of arterial and jugular venous blood, expressed in volumes per cent.

Changes in Oxygen and Carbon Dioxide Contents of Arterial and of Internal Jugular Venous Blood.—It was found impossible to withdraw frequent and simultaneous samples of arterial and of internal jugular venous blood during the course of the convulsion. In several instances, however, one or more samples were obtained from either the brachial artery or the internal jugular vein during and after the convulsion. In

4 instances it was possible to obtain simultaneous samples of blood from the artery and the internal jugular vein within one or two minutes after the convulsion.

A. Changes in the Arterial Blood: During the seizure there was observed a fall in oxygen content, which reached its lowest level at or shortly after the end of the convulsion (fig. 1 and table 1). With this change there was an increase in carbon dioxide content. That the oxygen returned quickly to its original level may be seen in cases 10, 11 and 12 (table 2), in which the blood was obtained within two minutes after the convulsion. At this time, that is, during the stage of hyperpnea, a gradual fall in carbon dioxide content occurred.

B. Changes in the Internal Jugular Venous Blood (tables 2 and 4): The changes in the gases in the blood of the internal jugular vein were

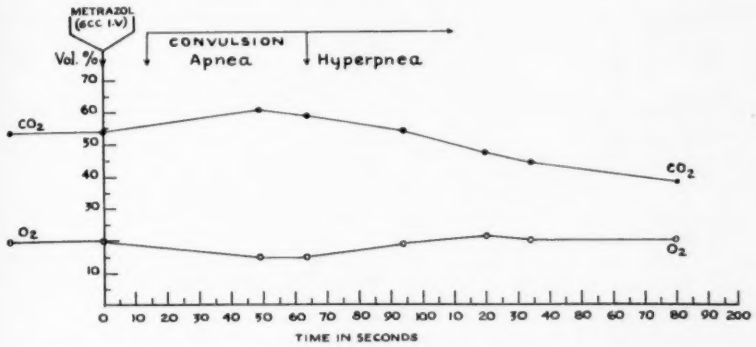


Fig. 1.—Effect of metrazol convulsion on the oxygen and carbon dioxide contents of the arterial blood, the maximum fall in oxygen and the greatest rise in carbon dioxide occurring near the end of the convulsion, followed by a rapid return of oxygen to normal and a gradual fall in carbon dioxide during and after the period of hyperpnea.

dependent on whether the blood was withdrawn immediately before, at the beginning of, during or after the metrazol convulsion. Thus, in 1 instance (fig. 2), in which samples of blood were withdrawn immediately after the injection of metrazol and at the beginning of the convulsion, no change in oxygen was evident. In 3 cases (nos. 10, 11 and 16), blood obtained at the beginning of the convulsion also showed no or very slight changes in oxygen. In 2 cases (nos. 15 and 17), when the blood was withdrawn within ten to fifteen seconds after the beginning of the seizure, diminution in oxygen was already apparent. As the convulsion progressed still further (cases 12 and 17 and fig. 2), it was evident from several consecutive samples withdrawn from the internal jugular vein that a gradual fall in oxygen occurred so that at the end of the convulsion, or some seconds later, this gas was at its minimum level. In 4 cases blood

removed within a minute or two after the convulsion showed an increase in oxygen above original levels, in 3 of them returning to, or closely to, the original values within approximately fifteen minutes. Thus, in 3 of the cases last mentioned, the difference in oxygen content of blood from the artery and that from the internal jugular vein was diminished and in the fourth case increased (cases 10, 11, 13 and 12, respectively). In another case the oxygen remained lower than the original level for ten minutes after the convulsion (table 2, case 15).

TABLE 3.—*Changes in Sugar in Arterial and Internal Jugular Venous Blood During Metrazol Convulsions*

Case	Time	Arterial Sugar, Mg./100 Cc.	Internal Jugular Sugar, Mg./100 Cc.	Difference in Arterial and Jugular Sugar Content of Venous Blood, Mg./100 Cc.
19	Before convulsion	110	84	26
	End of convulsion	132	109	23
20	Before convulsion	108	100	8
	End of convulsion	128	111	17
21	Before convulsion	70	60	10
	2 min. after convulsion	87	77	10
	18 min. after convulsion	110	102	8

TABLE 4.—*Changes in Oxygen and Carbon Dioxide Contents of Internal Jugular Venous Blood During the Various Stages of the Metrazol Convulsion (Case 18)*

Time	Oxygen Content, Vol. %	Carbon Dioxide Content, Vol. %	Comment
Basal	14.2	49.8	Before convulsion
0	....	....	Injection of metrazol (6 cc. intravenously)
20 sec.	....	....	Beginning of convulsion
57 sec.	11.6	52.8	Near end of convulsion
81 sec.	4.8	54.2	End of convulsion
85 sec.	10.0	50.1	Beginning of hyperpnea
150 sec.	16.3	38.2	End of hyperpnea
8 min.	16.1	26.0	Coma
13.5 min.	16.1	25.0	Semicoma

During the early stages of the convulsion, insignificant changes in carbon dioxide were present. With the fall in oxygen toward the end of the seizure this gas became increased, and as the hyperpnea progressed a gradual diminution in carbon dioxide occurred, which lasted for several minutes.

Alterations in Arterial and in Internal Jugular Venous Pressures.—Since it was impossible to obtain continuous indirect arterial readings during the convulsion, the direct intra-arterial method of Dameshek

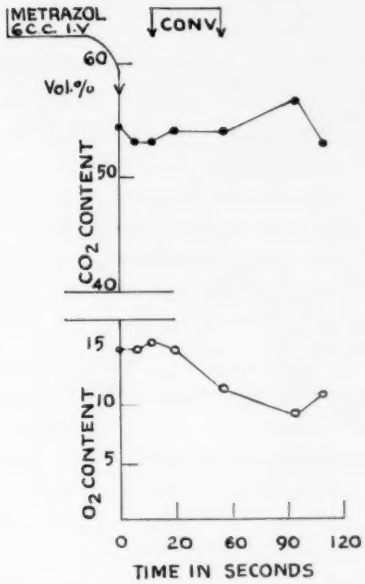


Fig. 2.—Effect of metrazol convulsion on the oxygen and carbon dioxide contents of the internal jugular venous blood for a period following the injection of the drug. There is no significant change in the oxygen immediately prior to and for the very first part of the convulsion. There follows a gradual fall in oxygen, which reaches a minimum about thirty seconds after the convulsion, at which time the carbon dioxide is at its height.

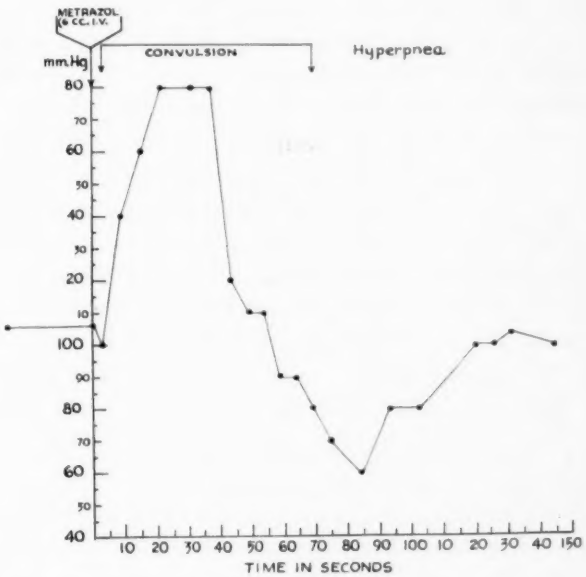


Fig. 3.—Variations in intra-arterial blood pressure during and after a metrazol convulsion. Note the secondary fall to a low level following the early marked rise in pressure.

and Loman [2] was utilized. Figure 3 shows the record of a case in which readings from the femoral artery were taken before and during the entire period of a convulsion. A marked, sharp rise occurred at the beginning of the seizure and was sustained for several seconds, followed by a fall to well below the original level toward the end of the convulsion, and finally by a gradual rise to normal.

In every case but 1, in which ordinary measurements of arterial blood pressure were made immediately after the convulsion, a sharp increase to hypertensive levels, lasting several minutes, occurred. One subject, who represented the exception, had circulatory collapse after the convulsion. During every seizure in which the jugular vein was punctured blood spurted from the vessel as though coming from an artery. In 1 case successful measurement of this pressure during the greater part of a convulsion showed a reading of 480 mm. of water.

COMMENT

Consideration of the changes in oxygen and carbon dioxide in the blood during metrazol convulsions must take into account the phenomena associated with apnea, hyperpnea, alterations in blood flow and blood pressure, not as separate events but as a complex series of changes occurring in the same person. Gibbs, Gibbs and Lennox [3] have demonstrated that immediately prior to spontaneous epileptic seizures or to those induced by hyperpnea the flow of blood through the brain did not decrease. During the seizures there was observed a marked increase in blood flow, which was interpreted as an effect rather than as a cause of the convulsion. These observations contradicted the theory that widespread cerebral anemia was the immediate cause of the seizures.

The fact that blood from the internal jugular vein collected immediately before or at the very beginning of the metrazol convulsion shows no significant changes in oxygen corroborates the conclusion of Gibbs and his associates regarding the immediate cause of the convulsion. Once the metrazol convulsion progresses, however, alterations in cerebral blood flow will depend on the state of the cerebral vessels, as affected by the gaseous concentration of the blood, and the level of the arterial blood pressure. Thus, the increase in carbon dioxide and the decrease in oxygen in the arterial blood during the asphyxial stage would in

2. Dameshek, W., and Loman, J.: Direct Intra-Arterial Blood-Pressure Readings in Man, Am. J. Physiol. **101**:140-147 (June) 1932.

3. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257 (Aug.) 1934.

themselves, as demonstrated by Gibbs, Gibbs and Lennox,[4] have the effect of increasing the cerebral blood flow, as a result of vasodilatation. This increase in blood flow may, however, temporarily be overcome by a marked fall in blood pressure, which may occur at the termination of a convulsion (fig. 3). That a fall in blood flow at this time occurs is further suggested by the sudden and added fall in oxygen content of the blood in the internal jugular vein (table 4). Marked falls in blood flow during metrazol convulsions in animals have been observed by Leibel and Hall,[5] who stated that the blood pressure was so low that no blood could be obtained from the ears of the animals. Gibbs[6] also found marked falls in cerebral blood flow following increase at the termination of convulsions induced in animals by means of various drugs.

Once the hyperpnea begins, rapid resaturation of the arterial blood with oxygen occurs, accompanied by pronounced lowering of the carbon dioxide. Such a marked fall in carbon dioxide should in itself have the effect of cerebral vasoconstriction, with consequent slowing of the cerebral blood flow.[4] Since, however, diminution in the difference between arterial and jugular venous blood usually occurs after the convulsion, some mechanism must compensate for the vasoconstricting effect of the hyperpnea. This mechanism may be the secondary rise in arterial blood pressure which usually takes place immediately after the stage of hyperpnea.

After the convulsion, an increase of oxygen in the blood from the jugular vein (diminished arterial-jugular difference) which usually occurs is not so great as or so prolonged as that reported in blood from the basilic vein (Steinfeld and Gerber[7]). That alterations in oxygen and carbon dioxide in the internal jugular and the peripheral veins do not necessarily parallel each other has been observed by Lennox and Gibbs[8]; Gibbs, Gibbs and Lennox[4]; Dameshek, Myerson and

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Physiol. **111**:557-563 (April) 1935.

5. Leibel, B., and Hall, E.: Physiological Studies in Experimental Insulin and Metrazol Shock: III. Cerebral Blood Flow Changes During Shock Therapy, Am. J. Psychiat. **95**:553-565 (Nov.) 1938.

6. Gibbs, F. A.: Cerebral Blood Flow Preceding and Accompanying Experimental Convulsions, Arch. Neurol. & Psychiat. **30**:1003-1010 (Nov.) 1933.

7. Steinfeld, J., and Gerber, L.: Oxygen Content of the Blood During the New Treatments for Schizophrenia, Illinois M. J. **72**:351-354 (Oct.) 1937.

8. Lennox, W. G., and Gibbs, E. L.: The Blood Flow in the Brain and the Leg of Man, and the Changes Induced by Alteration of Blood Gases, J. Clin. Investigation **11**:1155-1177 (Nov.) 1932.

Loman,[9] and Dameshek and Myerson.[10] A similar statement may be made in objecting to the theory of chronic hypoxia as a factor in dementia praecox (Hoskins[11]), a theory based partly on the oxygen and carbon dioxide values obtained from a study of the peripheral venous blood and partly on basal metabolic studies, neither of which sets of data reflects the specific changes occurring in the brain. Furthermore, the findings of Freeman[12] that the circulation time of schizophrenic persons is abnormally slow (with resulting deficiency in tissue respiration) have not been confirmed by Finesinger, Cohen and Thomson[13] and by Gottlieb.[14] It is still to be proved that defective oxygen metabolism is specifically related to the schizophrenic state.

All efforts to explain the similar clinical effects of insulin and of metrazol therapy on the common basis of changes in cerebral blood flow or changes in oxygen-sugar relationships fail when one examines critically the experimental data. During insulin hypoglycemia the increased oxygen of internal jugular venous blood is dependent not on changes in blood flow but on diminished uptake of oxygen consequent on deprivation of cerebral sugar (Dameshek and Myerson[10]; Loman and Myerson[15]). On the other hand, the changes in oxygen in the internal jugular vein during metrazol convulsions are directly related to the effects of asphyxia, and those following the convulsion, to changes in blood flow. Despite the marked alterations in oxygen during and after metrazol convulsions, there is usually a steady rise in sugar. Furthermore, in contrast to changes during the insulin reaction, there is no evidence of diminished uptake of sugar by the brain. Finally, marked asphyxia may occur without any change in the dextrose level of the blood.

Thus, there is little, if any, similarity between the cerebral hypoxia of insulin hypoglycemia and the hypoxia of a metrazol convulsion. Whether the brain of a patient with dementia praecox emerges the gainer from a short or long bout of hypoxia is questionable. Certainly,

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9. Dameshek, W.; Myerson, A., and Loman, J.: The Effects of Sodium Amytal on the Metabolism, Am. J. Psychiat. **91**:113-135 (July) 1934.

10. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: Mechanism of the Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1-18 (Jan.) 1935.

11. Hoskins, R. G.: Oxygen Metabolism of the Brain, Arch. Neurol. & Psychiat. **38**:1261-1270 (Dec.) 1937.

12. Freeman, H.: The Arm-to-Carotid Circulation Time in Normal and Schizophrenia Subjects, Psychiatric Quart. **8**:290-299 (April) 1934.

13. Finesinger, J. E.; Cohen, M. E., and Thomson, K. J.: Velocity of Blood Flow in Schizophrenia, Arch. Neurol. & Psychiat. **39**:24-36 (Jan.) 1938.

14. Gottlieb, J. S.: Arm to Carotid Circulation Time in Abnormal Mental States, Arch. Neurol. & Psychiat. **41**:1117-1126 (June) 1939.

15. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Craniovertebral Cavity, Am. J. Psychiat. **92**:791-813 (Jan.) 1936.

the theory of defective oxygen metabolism as a cause of dementia praecox is open to great doubt, for it is difficult to conceive that if such a faulty mechanism underlies this condition, it can be permanently overcome by any transient disturbance of the brain produced by insulin hypoglycemia or metrazol convulsions. The theory of cerebral hypoxia might be more aptly applied to the affective psychoses, if one accepts the superior therapeutic results of metrazol therapy reported for this group of mental states (Low and his associates,[16] Bennett [17] and Cottington and Gavigan [18]). Any improvement seen in dementia praecox after metrazol therapy may, in the present chaotic state of knowledge, best be considered an induced interlude in a disease which in its earlier stages of evolution is still relatively "reversible." The mechanism by which insulin hypoglycemia or metrazol therapy brings about such improvement is still unknown.

SUMMARY AND CONCLUSIONS

Changes in the oxygen, carbon dioxide and sugar contents of blood from the basilic vein, the internal jugular vein and the brachial artery were followed in a group of subjects with dementia praecox in whom convulsions were induced with metrazol. The following observations were made:

A. Changes in Basilic Venous Blood.—1. The oxygen content becomes lowered as the convulsion progresses, reaching its lowest levels near the end of the seizure and quickly returning to basal or higher than basal levels soon after the convulsion.

2. Sugar gradually increases as the convulsion progresses, usually reaching its highest levels some time after the convulsion.

B. Changes in Arterial and Internal Jugular Venous Blood.—1. A gradual fall in oxygen with a rise in carbon dioxide occurs in the arterial blood during the convulsion, these changes being most marked at the end or soon after the end of the seizure. The oxygen quickly returns to original levels within a few minutes after the convulsion, at which time the carbon dioxide gradually diminishes during the stage of hyperpnea.

2. Blood collected from the internal jugular vein immediately before or at the very beginning of the convulsion is unchanged in oxygen and

16. Low, A. A.; Sonenthal, I. R.; Blaurock, M. F.; Kaplan, M., and Sherman, I.: Metrazol Shock Treatment of the "Functional" Psychoses, Arch. Neurol. & Psychiat. **39**:717-736 (April) 1938.

17. Bennett, A. E.: Convulsive Pentamethylenetetrazol Shock Therapy in Depressive Psychoses, Bull. Menninger Clin. **2**:97-100, 1938.

18. Cottington, F., and Gavigan, A. J.: Metrazol Treatment of Depressions, New England J. Med. **220**:990-992 (June 15) 1939.

carbon dioxide content. As the convulsion progresses, the oxygen content gradually diminishes, so that at the end of the seizure it is at its lowest level. At this time the carbon dioxide content is increased. During the stage of hyperpnea the oxygen quickly returns to original or higher than original levels, while the carbon dioxide gradually falls.

3. An increase in sugar usually occurs as the convulsion progresses, with little change in the difference between arterial and internal jugular venous blood.

These data support the following comments: Although local cerebral vasoconstriction may immediately precede a metrazol convulsion, there is no evidence from these studies that cerebral anemia initiates the seizure. As the convulsion progresses, however, a change occurs in cerebral blood flow, dependent on the altered relationship of blood gases and changes in blood pressure. Any change in cerebral blood flow following the convulsion is temporary, as indicated by the return of blood gases to original levels within a short time after the convulsion. There is no similarity between insulin hypoglycemia and a metrazol convulsion as regards changes in the relationship of dextrose and oxygen. The cerebral hypoxia occurring in the former condition has only a superficial resemblance to the cerebral hypoxia of the latter condition. So far as these data are concerned, changes in mental states following metrazol convulsions and insulin hypoglycemia cannot be explained on the basis of any common alteration in either cerebral chemistry or cerebral blood flow.

INVESTIGATION OF ELECTROLYTIC RECTIFICATION IN NERVES

INVALIDITY OF PFLÜGER'S LAW OF CONTRACTION

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AND
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When a nerve impulse which causes a contraction of an associated muscle is produced by the closing of an external galvanic circuit with the nerve in series, it is said to arise as the cathode, while that produced by the opening of the external circuit is initiated at the anode. It has been held, prominently by Pflüger, that when "very strong" currents are used in an ascending direction, i. e., away from the muscle, no contraction occurs on the closing of the circuit since the impulse is blocked at the anode by the depressed conductivity caused by electrotonic changes, and that when the current is descending, i. e., toward the muscle, no contraction occurs on the opening of the external circuit because of a similar blocking at the cathode.

When we repeated the experiments on the basis of which Pflüger's law was postulated, the results were variable. Although it was found to be true that when a strong current was used for the first stimulus a contraction may have occurred on closing and not on opening the circuit, or the reverse, the efficacy of the stimuli did not hold a constant relationship to the direction of the current.

Since various parts of the apparatus, including the frog holder, were made of metal, it was thought that the apparatus may have acquired an electrostatic charge which was of sufficient magnitude to have been responsible for the erratic contractions referred to. If such was the case, we should be able to reproduce the phenomena by stimulating the nerve by means of currents produced by residual electrostatic charges.

Recently, Brickner and Grant [1] have described the contractions produced in a muscle when its nerve is placed within the magnetic flux

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Read at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 5, 1939.

1. Brickner, R. M., and Grant, R. E.: Electrical Stimulation of a Nerve Muscle Preparation Without Contact, Proc. Soc. Exper. Biol. & Med. **32**:1240, 1935.

produced by energizing a coil consisting of a number of turns of insulated wire, when the energizing circuit of the coil is closed or is opened. The effect on nerves of supposed electromagnetic stimulation by magnetic fields was observed and studied many years ago (Heidenreich,[2] Hermann[3]). Whether the effects were due to electromagnetic or to electrostatic currents has been a matter of controversy.

METHODS AND RESULTS

When we stimulated a nerve placed in the core of a coil wound with 5,500 turns of no. 40 wire, energized from a battery supplying 30 volts at 2.5 milliamperes, we observed that when a contraction ensued on closing the circuit through the coil it did not occur on opening it. When the muscle-nerve preparation was grounded, the response to the stimulation became much stronger, and less current was required to initiate a contraction. When a coil was electrostatically shielded and this shielding grounded, no response could be obtained either on closing or on opening the circuit even when the energizing potential difference was increased to 150 volts. From this we concluded that the response was due to an electrostatic current, and since the direction produced by closing the circuit was opposite that produced by opening the circuit, it was thought that the nerve acted as a rectifier, permitting unidirectional flow of current through the preparation.

This was found to be true when the nerve was stimulated by the discharge of a condenser. With a condenser having a capacitance of 0.0003 microfarad charged in a certain direction to a difference in potential of 1.13 volts, it was found that when the condenser was discharged a contraction ensued, but that when it was charged in an opposite direction and discharged no contraction occurred. The efficacy of the discharge required to produce contraction did not depend on the direction of current in relation to the nerve-muscle preparation. The condenser discharge produced a contraction in some preparations when it resulted in an ascending current and in others when it resulted in a descending current. Since in each discharge there is a make and a break of the current, failure to produce a contraction cannot be explained on the basis of polar electrotonus.

We attempted to reduce the possibility of stray electrostatic currents in subsequent experiments in the following manner: On one table were arranged the parts of the circuit needed for the stimulating apparatus, the voltage divider, the noninductive variable resistor, the reversing switch and the necessary keys. The side of the circuit connected with the nonpolarizable electrodes in contact with the nerve was grounded; all the connections were soldered. On another table, insulated by glass legs, rested a small wooden table on sulfur blocks. The boot electrodes were mounted on a glass and ebonite support resting on a plate glass table top, and the zinc electrodes were surrounded by a glass tube open at the bottom before being placed in the boots. The leg of the frog was supported by cork. Under the conditions outlined, it was found that the contractions resulting from closing and opening the external circuit did not follow Pflüger's law.

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2. Heidenreich, F. W.: Die physiologische Induktion, ein Beitrag zur medizinischen und Nerven-Physik, Ansbach, E. H. Gummi, 1846; cited by Hermann.[3]

3. Hermann, L.: Hat das magnetische Feld directe physiologischen Wirkungen? Arch. f. d. ges. Physiol. **43**:217, 1888.

It was found that whereas at first contractions of varying strength, even tetanus, occurred only on the closure of the circuit (make), these contractions successively became more and more feeble and finally disappeared altogether. At the same time, whereas at first no contractions resulted from opening the circuit (break), they appeared, became stronger and stronger and were at times tetanic. This mutation of response occurred whether the nerve was stimulated by a "descending" or an "ascending" current (fig. 1).

When the voltage of the first stimulus was low, 0.02 volt, and the voltage of each succeeding stimulus was increased by 0.02 volt, at some point, say 0.06 volt, a contraction occurred on closing the circuit but not on opening it; as succeeding stimuli of increasing voltage were applied, these contractions became stronger and stronger until a point was reached, let us say at 0.22 volt, at which a feeble

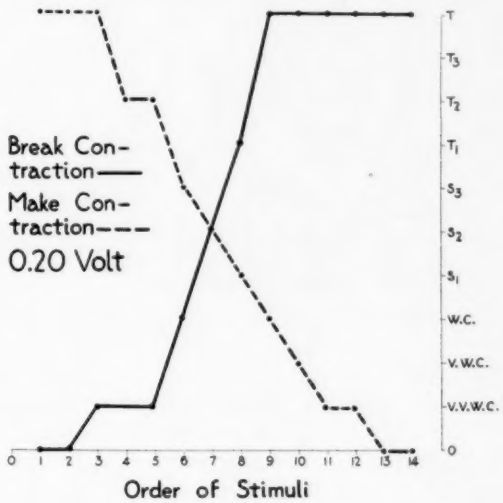


Fig. 1.—Relation of reciprocal efficacy and inefficacy of make and break stimuli after repeated stimulation.

In this figure and in figures 2, 3 and 5, the following abbreviations are used: *O*, no contraction; *V.V.W.C.*, very, very weak contraction; *V.W.C.* very weak contraction; *W.C.*, weak contraction; S_1, moderate contraction; S_2, stronger contraction; S_3, strong contraction; T_1, slight tetanus; T_2, moderate tetanus; T_3, strong tetanus, and *T*, strong and prolonged tetanus.

contraction also appeared on opening the circuit; from this point the contractions on opening the circuit became stronger and stronger, whereas those occurring on closing it became weaker and weaker and disappeared. This mutation of response also occurred irrespective of the direction of the current ("ascending or "descending"; fig. 2).

In the same preparation, when successive stimuli in only one direction were used, it occasionally was found that at first contractions occurred only on the make and became progressively weaker, then appeared on the break and reached a point at which tetanus occurred on the break and no contractions appeared on the make. Then if stimulation was continued there was a reversal of this reciprocal

relationship, the contractions on the break becoming weaker and disappearing and the contractions on the make appearing and becoming stronger and stronger (fig. 3).

That the direction of the current seemed to be unrelated to the efficacy of make and break stimuli and that repeated or prolonged stimuli produced a

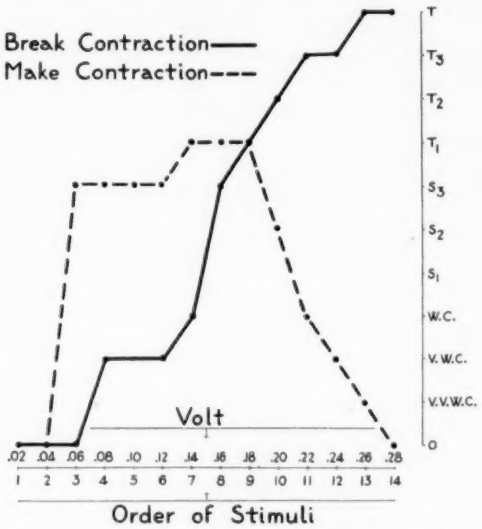


Fig. 2.—Response to repeated make and break stimuli of increasing voltage.

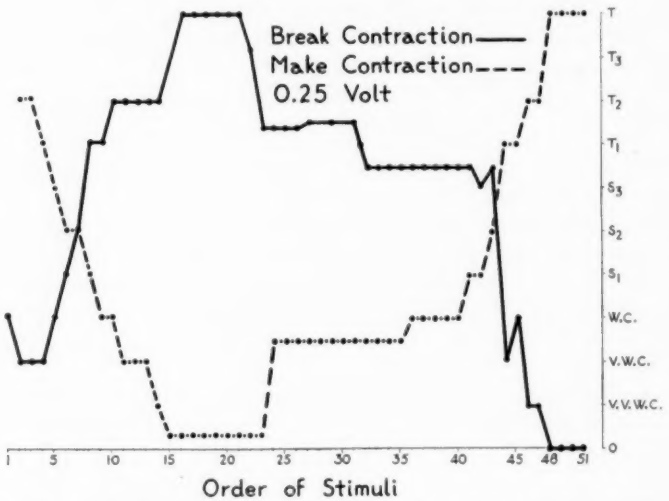


Fig. 3.—Reversal of the relative efficacy of make and break stimuli after continued successive stimuli.

reversal of their reciprocal efficacy suggested that in the changes in polarization occurring in a nerve we were dealing with amphoteric electrolytes.

This was shown to be a fact by measuring the changes produced in the so-called after-current following repetitive or long-continued stimulation. As

early as 1834, Peltier discovered that in frog limbs, or even in isolated pieces of muscle, an "after-current" developed in the direction opposite that of stimulation. Du Bois-Reymond [4] advanced the idea that this after-current was the result of internal polarization and attributed it to electromotive molecules which were homodromously adjusted with the primary current; Hering [5] and Hermann,[6] however, adduced proof that the changes occurred only at the physiologic poles and were due to localized anode effect. In conformity with our findings, Hering showed that the current measured prior to excitation showed after excitation an increase or decrease, neutralization or reversal.

When after each of successive stimulations we measured the current between the nonpolarizable electrodes on the nerve, we found that, beginning with no current, each successive stimulus produced a change in polarization (presumably in the tissue, since the electrodes were relatively nonpolarizable) usually in one

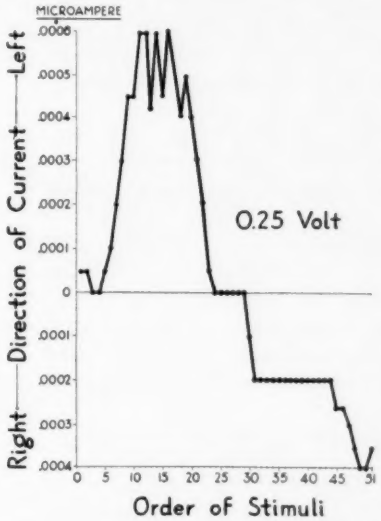


Fig. 4.—Reversal of polarity of the output of the "after-current" after repeated stimuli in the same direction.

direction, negative or positive, irrespective of whether the stimulating current was ascending or descending. Beginning with zero, the output of the after-current could be increased to as high as 0.0015 microampere after ten stimuli of ten seconds' duration with a current of 0.2 volt.

On rare occasions it was observed that the after-current increased in one direction up to a certain point, then diminished progressively to zero, changed its polarity and increased progressively in the opposite direction (fig. 4).

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4. Du Bois-Reymond, E.: Ueber secundär-elektromotorische Erscheinungen an Muskeln, Nerven und elektrischen Organen, Sitzungsber. d. k. preuss. Akad. d. Wissensch. **16**:343, 1883.

5. Hering, E.: Ueber das electromotorische Verhalten curarisierter Muskeln nach galvanische Durchströmung, Arch. f. d. ges. Physiol. **58**:133, 1894.

6. Hermann, L.: Ueber sogenannte secundär-electromotoriche Erscheinungen an Muskeln und Nerven, Arch. f. d. ges. Physiol. **33**:103, 1884.

This shows that the electrolytes of a nerve are amphoteric. Since the relative efficacy of make and break stimuli depended on changes in polarization produced by preceding stimuli and since the direction of the stimulating current had no relation to the polarity of the after-current, we concluded that the direction of the stimulating current, ascending or descending, was unrelated to the reciprocal efficacy and inefficacy of make and break stimuli.

Erlanger and Blair [7] studied the changes in the configuration of the action potential when the nerve, the phalangeal preparation, was polarized continuously at the lead, sometimes cathodally, sometimes anodally. They found when the proximal lead was polarized anodally and the action potential was monophasic, since the distal electrode was placed on a killed portion of the nerve, that with increase in polarization the action potential became lower and lower and finally was so weak that it could scarcely be distinguished from the noise level of the amplifier. When both leads were on intact nerve and the anode was the proximal lead with respect to the stimulated point, the negative part of the diphasic potential changed as in the preceding experiment; it became higher, a notch developed, and the upper element suddenly dropped out, leaving a lower spike; at the same instant the positive element also disappeared.

Erlanger and Blair concluded that their results were accounted for through the establishment of localized seriatim blocks. This blocking, they thought, was comparable with that occurring in the classic experiment of Pflüger.

This may be an explanation for the reciprocal efficacy and inefficacy of make and break stimuli, but does not itself support the validity of the conception of the relation of "ascending" and "descending" currents to this reciprocal efficacy and inefficacy. On the other hand, at the time when, in their experiments, the upper element of the negative part of the diphasic potential suddenly dropped out, leaving a lower spike, and at the same time the positive element disappeared and the record became completely monophasic, the effect was analogous to half-wave rectification.

Attention was next directed to the cause of the break contractions.

A nerve will respond only to a transient potential, not to a steady state of stimulation by a potential. It has been assumed, among other explanations, that the nerve fails to respond to continuous stimulation because of its rapid adaptation. The cause of the contraction occurring on the break of a stimulating current has been attributed by Peltier, Matteucci, Tigerstedt,[8] Grützner,[9] Hoorweg [10] and others to negative polarization currents which, when the stimulating circuit is opened, discharge through the nerve itself. To this conception Du Bois-Reymond objected and stated that "these changes in order to induce a current through the nerve required to all appearance a closed circuit, which condition was canceled by opening it." In our experiments it was found that strong break contractions occurred when no after-current was present. We therefore sought for some other explanation of the break contraction. It will become evident that, in addition

7. Erlanger, J., and Blair, E. A.: Manifestations of Segmentation in Myelinated Axons, Am. J. Physiol. **110**:287, 1934.

8. Tigerstedt, R.: Zur Theorie der Öffnungzuckung, Mitth. v. physiol. Lab. d. Carolin. med.-chir. Inst. in Stockholm, 1882, no. 2, p. 1; cited by Grützner.[9]

9. Grützner, P.: Beiträge zur allgemeinen Nervenphysiologie; über das Wesen der elektrischen Offnungserregung, Arch. f. d. ges. Physiol. **32**:357, 1883.

10. Hoorweg, J. L.: Ueber die electrische Nervenerregung, Arch. f. d. ges. Physiol. **53**:587, 1893.

to a "negative polarization" or after-current developing after continued or repeated stimulation, the nerve acquires ability to hold a charge put on it by the stimulating current. This charge, when the stimulating circuit is opened, can be discharged through a ballistic galvanometer and measured. After its discharge the after-current remains as a residual current.

By means of a charge and discharge key, on closing the circuit a current from a battery was conducted through the nerve of a nerve-muscle preparation, and when this circuit was opened another circuit was closed through a galvanometer, discharging and measuring any charge put on the nerve by the stimulating circuit. An ultrasensitive direct current galvanometer,[11] having a sensitivity of 0.0004 microampere per scale division, was used as an indicator. The discharge

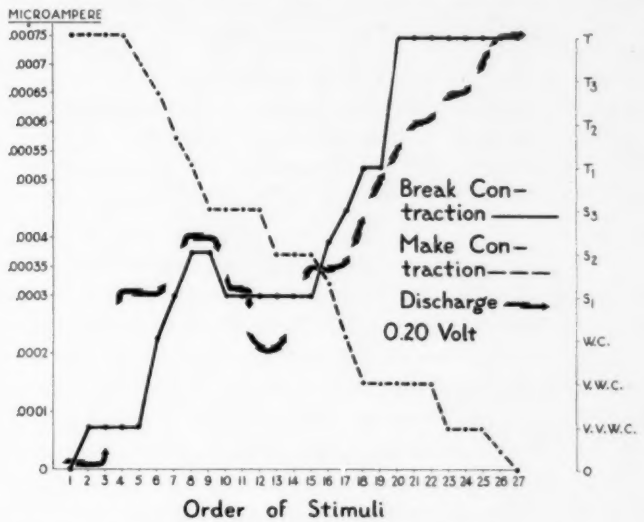


Fig. 5.—Relation of the quantity of discharge of the charge put on a nerve by the stimulating current to the efficacy of make and break stimuli.

of a condenser having a capacity of 0.005 microfarad charged to a potential difference of 0.2 volt produced a throw equivalent to the reading of 0.0004 microampere. After the first stimulus occurring when the circuit was closed, little or no current was discharged when it was opened. With succeeding stimuli, discharges appeared and progressively increased in quantity. After ten successive stimuli of 0.2 volt each for ten seconds, there may be a throw equivalent to a reading of 0.0010 microampere or more.

As the size of the discharge increased, contractions which had occurred only on closing the circuit now began to appear on opening the circuit, and continued to increase in intensity as the discharges became larger and larger.

Acting at first as an electrolytic conductor, the nerve behaved as an electrolytic condenser in the process of formation, developing greater and greater ability to hold a charge with increase in number or duration of stimuli. To meet the objection proposed by Du Bois-Reymond that it is necessary to have a closed

11. Ultrasensitive D-C Meter, Stock no. 9819, Ml-7521, R. C. A. Manufacturing Co., Inc.

circuit to effect a discharge through the nerve and that when the stimulating circuit is opened no closed circuit remains, it may be said that when the galvanometer circuit is closed only after a contraction has occurred on the break of the stimulating circuit there is no discharge through the galvanometer, the charge apparently being dissipated between what is equivalent to two plates of a condenser through an imperfect dielectric. It is suggested that the contractions resulting from opening a circuit (break contractions) are related to the discharge of a charge put on the nerve when the stimulating circuit is closed.

As the discharges became larger and larger and the break contractions appeared and progressively became stronger, the make contractions, which were at first strong, became weaker and weaker and disappeared, irrespective of whether the current was ascending or descending (fig. 5).

Various known electrolytic condensers are also electrolytic rectifiers. During the formation of an electrolytic condenser its forward conductance is diminished. Since during the discharge the flow of current is in a direction opposite that of the charge, it is suggested that when successive or prolonged stimuli produce in a nerve an effect analogous to those known to exist in the case of an electrolytic condenser, stimuli in the direction of the charging current, produced by closing the stimulating current, are rectified, and thus no contraction results.

SUMMARY

When the experiments on the basis of which Pflüger's law of contraction was postulated were repeated, the results were variable: At times, with a strong descending current, a contraction occurred on the make and not on the break; at other times, the contraction occurred on the break and not on the make. Since it was believed that the contractions probably were the result of stimulation by stray electrostatic fields or currents, experiments were performed to study the response of a nerve to stimulation by currents produced by the discharge of a condenser and stray electrostatic fields developed within a coil. In both instances, within certain limits, an effect similar to rectification was observed; when the nerve responded to a wave in one direction it did not respond to one in the opposite direction, irrespective of whether, in relation to the nerve, the current was ascending or descending. When, by suitable apparatus and circuits, the possibility of stray electrostatic currents was diminished, the nerve did not respond to make and break stimuli in accordance with Pflüger's law. Now, uniformly, a contraction followed each first few make stimuli, irrespective of voltage or direction of current.

In the same preparation, when successive stimuli in only one direction were used, a reversal of the reciprocal relationship between the efficacy of make and of break contractions could be brought about. At the same time, when the output of the after-current was measured, it was found that as the stimuli were continued the output increased to a certain point, then progressively diminished to zero, changed in polarity and progressively increased in the opposite direction. Since the last two

observations show that the electrolytes of a nerve are amphoteric, the relative efficacy of make and break stimuli could not be related to the direction of the stimulating current, ascending or descending, or the inefficacy of a make or break stimulus to polar electrotonus.

By means of a charge and discharge key, on closing the circuit, the current from a battery was conducted through a nerve, and when this circuit was opened another circuit was closed through a galvanometer, discharging and measuring the charge put on the nerve by closing the stimulating circuit. It was found that at the first opening of the circuit little or no electricity was discharged, but that with successive stimuli the nerve acted as an electrolytic condenser in the state of being formed and acquired increasing ability to hold a charge. As the size of the discharges increased, contractions appeared on opening the circuit and successively became greater and greater. It is therefore suggested that the contractions resulting from opening a circuit are related to the discharge of a charge put on the nerve when the stimulating circuit is closed. As the discharges became larger and larger and the break contractions stronger and stronger, the make contractions which were strong became weaker and weaker and finally disappeared. An electrolytic condenser is also an electrolytic rectifier, and as its ability to hold a charge increases, so does its forward conductance diminish. It is suggested that when successive or prolonged stimuli produce in the nerve an electrolytic rectifier of sufficient efficiency, stimuli in the direction of the charging current produced by closing the stimulating circuit are rectified and thus no contraction results.

CONCLUSIONS

With circuits designed to diminish stray electrostatic currents, we were unable to confirm Pflüger's law of contraction.

Within certain limits there is a rectification effect in nerves stimulated by electrostatic currents produced by condenser discharges or electrostatic fields in a coil.

Repetitive or long-continued galvanic stimuli produce changes in polarization which are amphoteric, and therefore the inefficacy of a make or break stimulus cannot be related to the direction of the current, ascending or descending.

The contraction occurring as the result of opening a galvanic circuit (break) is related to the discharge of a charge put on the nerve when the circuit is closed.

The failure to obtain a make contraction when a break contraction is obtained is due to electrolytic rectification, the nerve being formed into an electrolytic rectifier by repetitive or prolonged galvanic stimuli.

Mr. Charles M. Wilson gave technical assistance and suggestions.

DISCUSSION

DR. DETLEV W. BRONK, Philadelphia: In addition to the general conclusions, which need no further comment, there are two aspects of this paper that interest me. The first is the emphasis which Dr. Pollock has given to the necessity for caution when studying experimentally the response of nerves to electrical stimuli. Because of its high degree of irritability, nerve tissue is capable of responding to weak currents, and stray electrostatic current can therefore be an obscure source of artefacts and consequent error. Such frequently unrecognized pathways for stimulating currents are over the surface of materials and also through a leakage capacitance.

I was also pleased to hear Dr. Pollock stress the importance of previous activity as a factor which modifies the properties of nerve. The experimental neurologist must ever remain alert to the realization that the characteristics of nerves are constantly varying, not only as a result of changes in the composition of the environmental fluids but also in consequence of the preceding activity of the neurons. Gasser and his colleagues and investigators in the laboratories of the Johnson Foundation are again emphasizing the fact and demonstrating the long-lasting results of the conduction of a train of impulses.

I should like to ask Dr. Pollock to explain in somewhat more detail the role of amphoteric electrolytes to which he referred, for I did not understand the mechanism. Finally, may I ask whether Dr. Pollock has tried different types of nerves? Specifically, I have in mind the question of the possible role of the myelin sheath in the electrical process with which he is dealing.

DR. RALPH W. GERARD, Chicago: Dr. Pollock and Dr. Finkelman have certainly entered into a field of the utmost importance in neurophysiology. The question of polarization, potentials and electrotonic potentials is coming more and more into prominence, as was foreshadowed in some of the discussion this afternoon. The current picture of nerve activity depends on the concept of an initially polarized membrane, polarization of which is broken down in the course of stimulation. Since the initial charge has a definite direction, the effectiveness of an electric stimulus should depend on the direction of the applied voltage.

In addition to the immediate effect on the nerve of an applied potential, there are now the well recognized afterpotentials, which modify activity and threshold and which, as Dr. Bronk has indicated, change markedly with the previous activity of the neurons. The postpolarization change, or postcathodal depression, for example, is related to the refractory period and also changes with repeated activity; it has been recently suggested that the summation of separate afferent impulses on a single neuron in a pool may depend partly on the spread of electrotonic potentials between the separate end feet of the single cell.

It has been known since the last century, from the work of von Fleishl, that passing currents through a nerve, even though the currents are symmetric and alternating, might produce a directional potential by a sort of rectification. That seems to have been related, however, to the sheath of the nerve trunk and, perhaps in part, to the myelin sheaths of the individual fibers rather than to an effect unique to and significant for the excitation of the individual nerve fiber.

I am not entirely clear about some of the observations that have been reported. They seem to be significant in showing a reversal of make and break responses and as such will certainly have to be taken into consideration by the neurophysiologist. I do not know whether the authors intended to imply that so far as the single nerve fiber is concerned excitation may be equally achieved by a current running into the fiber from the outside or running out of the fiber from

the inside. I imagine they did not, for there is much experimental material on the phenomena of excitation to a directional polarization, and these are further in satisfactory quantitative agreement, with theoretic equations which demand directional differences across the axon membrane.

DR. LEWIS J. POLLOCK, Chicago: I am neither a physiologist nor an electrophysicist. In the third year of my course in neurology it was necessary for me to review the subject of electrophysiology. At this time I am confronted by such terms as demarcation current, negative variation, catelectrotonus, anelectrotonus and Pflüger's law of contraction. When I compare this terminology with that in use by modern electrophysicists and electrochemists, it is almost incomprehensible. It is a nomenclature that developed chiefly along philosophic lines after the discovery by Galvani of the asymmetric potentials originating at the junction of electrodes with injured and uninjured portions of nerve and muscle. On the other hand, after Volta recognized the true significance of the asymmetric potentials and constructed the voltaic cell, the nomenclature of the physicist developed along independent and physical lines.

The electrolytes in the nerve-muscle preparation seem to me to be amphoteric, since with a constant direction of current they may at first assume an orientation, for instance, to the positive pole and then, with the continuation of this same direction of current, reverse and go to the negative pole, evidencing a change in polarity. It was particularly this observation which led us to believe that Pflüger's law was invalid, since if by means of polarization changes under a cathode or other electrode produced an inhibition, diminished conductivity or irritability which was responsible for reciprocal efficacy and inefficacy of make and break stimuli, then one would expect these polarization changes to be constant and unidirectional and not to reverse themselves.

We have not studied any different nerves than this one of the frog. I have not the slightest doubt that Dr. Bronk is correct in saying that they will all respond in a different manner. Not only should we expect different nerves to respond differently, but we should also expect different responses from different solutions containing electrolytes. In fact, it does not appear to us that we are studying the physiology of nerves when, after having produced asymmetric potentials at the junction of electrodes with injured and uninjured portions of nerve and muscle, we then attempt to modify them by unphysiologic stimuli.

The same interpretation may be applied to the creation by repeated electric stimuli of a condition in a nerve which is responsible for the reciprocal efficacy and inefficacy of make and break stimuli. This difference in response is not related to the direction of the stimulating current but to something artificially produced in the nerve. Similar conditions of rectification can be brought about in cells with certain electrodes and electrolytic solutions.

Modern electrophysiologists, of course, employ impeccable methods, but the conditions they are studying are not, we believe, primarily concerned with our problem.

It is quite possible that the time rate of excitation is one of the things with which we are concerned, since as an increase of impedance develops in the forward direction, the less acute will be the slope of change of electric potential difference.

We have not carried out any experiments on single nerve fibers.

ACTION POTENTIALS OF MUSCLES IN RIGIDITY AND TREMOR

PAUL F. A. HOEFER, M.D.
AND
TRACY J. PUTNAM, M.D.
NEW YORK

Rigidity and alternating tremor of antagonist muscles are the two presenting symptoms of paralysis agitans, whether of the senile (usually arteriosclerotic) or of the juvenile and presenile (usually postencephalitic) type. Either symptom may exist without the other, or either one or both may be unilateral or restricted to a single extremity. Rigidity may imitate the spasticity of patients who suffer from hemiplegia or paraplegia, and though voluntary movement is usually possible, the motor performance of patients afflicted with rigidity may for practical purposes amount to "unmistakable paresis," as Foerster has expressed it.[1] Tremor and rigidity exist in conditions other than paralysis agitans. They appear, however, to be linked in this disease in a specific way. It has been one of the purposes of this investigation to elucidate the underlying mechanism of this linkage. Rigidity, tremor and reflexes under various conditions were therefore studied by means of electromyography. Studies of the management of normal [2] and of spastic movement [3] by the same method have previously been reported.

METHOD AND MATERIAL

Action potentials of whole muscles in surface leads and of motor units or small groups of units in coaxial needle electrode leads were recorded with a cathode ray oscillograph, or with a six channel ink-writing oscillograph for simultaneous independent tracings from different structures.[4]

This is the third of a series of clinical and experimental studies of motor disorders.

From the Department of Nervous and Mental Diseases, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

1. Foerster, O.: Zur Analyse und Pathophysiologie der striären Bewegungsstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:1, 1921.

2. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201 (Aug.) 1939.

3. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in "Spastic" Conditions, Arch. Neurol. & Psychiat. **43**:1 (Jan.) 1940.

4. Dr. F. A. Gibbs and Dr. William G. Lennox permitted us to use the ink-writing oscillograph.

Electromyograms of 38 patients and of several otherwise normal subjects with "essential" tremor were studied for this report. Two of the patients presented cerebellar tremor and one a picture resembling decerebrate rigidity. Clinical data concerning the patients will be found in the accompanying table.

Clinical Data on Patients

Current No.	Initials	Age, Years	Diagnosis	Symptoms
1	R. G.	42	Postencephalitis	Rigidity
2	C. S.	30	Postencephalitis	Rigidity
3	I. D.	57	Paralysis agitans	Rigidity and tremor
4	E. T.	55	Paralysis agitans	Rigidity and tremor
5	J. R.	54	Hemiparalysis agitans	Rigidity and tremor
6	T. K.	19	Postencephalitis	Rigidity, tremor and residual chorea
7	M. McF.	74	Hemiparalysis, paralysis agitans	Rigidity and tremor
8	G. N.	57	Paralysis agitans	Rigidity and tremor
9	J. H.	39	Post-traumatic parkinsonism	Unilateral tremor
10	M. M.	60	Paralysis agitans	Rigidity and tremor
11	L. C.	32	Postencephalitis	Unilateral rigidity and tremor
12	J. S.	55	Hemiparalysis agitans	Tremor
13	E. J.	44	Postencephalitis	Unilateral rigidity and tremor
14	F. McK.	32	Postencephalitis	Rigidity and tremor
15	A. D.	58	Paralysis agitans	Rigidity and tremor
16	C. H.	38	Postencephalitis	Unilateral rigidity
17	T. B.	39	Postencephalitis	Rigidity and tremor
18	E. K.	50	Hemiparalysis agitans	Rigidity and tremor
19	M. R.	55	Paralysis agitans	Rigidity and tremor
20	P. G.	49	Postencephalitis	Rigidity
21	H. O'B.	21	Postencephalitis	Rigidity
22	E. S.	49	Postencephalitis	Unilateral rigidity and tremor
23	L. S.	55	Hemiparalysis agitans	Rigidity and tremor
24	J. G.	35	Postencephalitis	Unilateral rigidity and tremor
25	T. S.	19	Postencephalitis	Unilateral tremor
26	F. S.	67	Hemiparalysis agitans	Tremor
27	R. D.	35	Postencephalitis	Rigidity and tremor
28	K. McA.	56	Hemiparalysis agitans	Tremor
29	M. W.	55	Hemiparalysis agitans	Rigidity and tremor
30	N. D.	32	Postencephalitis	Rigidity
31	D. S.	25	Postencephalitis	Rigidity
32	L. B.	33	Postencephalitis	Rigidity
33	F. B.	70	Paralysis agitans	Tremor
34	C. B.	45	Postencephalitis	Unilateral rigidity and tremor
35	G. S.	36	Post-traumatic parkinsonism	Unilateral rigidity and tremor
36	S. M.	68	"Decerebrate rigidity"	
37	M. C.	58	"Lateral medullary syndrome"	"Cerebellar" tremor
38	G. K.	37	Multiple sclerosis	"Cerebellar" tremor

RESULTS

Voluntary Movement.—Voluntary movement in parkinsonian states may vary from almost normal performance to almost complete incapacity. The strength and range of motion available may also be little or much affected.

A group of observations showing the disturbance of voluntary movement in progressive order is presented in figure 1. These records were obtained with

the cathode ray oscillograph from whole muscles (flexors and extensors of the upper and the lower portion of the arm) by means of surface electrodes. Two of the patients selected had generalized tremor with rigidity (fig. 1 *A*, *C* and *D*); 2 had rigidity alone (fig. 1 *B* and *E*).

The first record (fig. 1 *A*) is most nearly normal.[2] An obvious pattern of tremor is seen, however, while frequency and amplitude are within normal limits. In *B* and *C* the change is more marked, as the pattern becomes predominant. Instead of a continuous sequence of tall spikes the action potentials are grouped in bursts at a rate of about 6 a second, while smaller potentials apparently keep

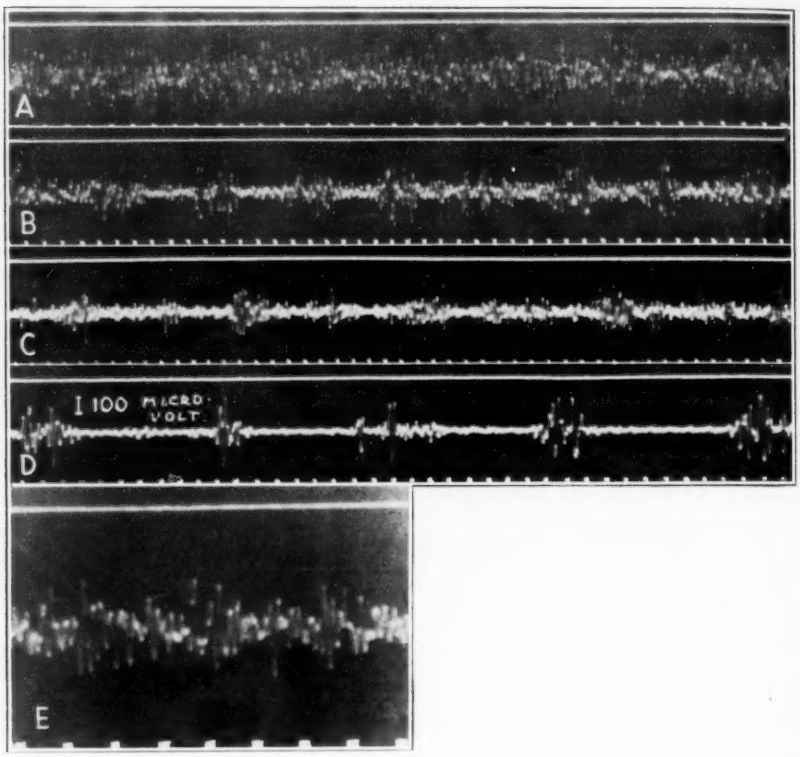


Fig. 1.—Voluntary contraction of rigid muscles in surface leads. Time: one-sixtieth second between flashes. Calibration in microvolts given in *D*. Cathode ray oscillograph. *A* (patient 4), flexors of the forearm; *B* (patient 2), extensors of the forearm; *C* (patient 3), one electrode on the flexor group and one on the extensor group of the forearm, making a fist; *D* (patient 3), one electrode on the biceps and one on the triceps muscle, with the half-bent arm extended against resistance, and *E* (patient 1), biceps muscle, enlarged. *A*, *C* and *D* represent patients with rigidity and tremor; *B* and *E*, patients with rigidity without tremor. Note progressive discontinuation of the influx impulses.

up the continuity of innervation between them. In *D* the continuous sequence is abolished and replaced by discrete bursts of spike potentials separated by stretches of electrical inactivity. This progression is parallel to an increasing staccato

quality of the movement. In its extreme (fig. 1 *D*) the pattern is similar to that of tremor (see page 710). The inequality of the potential sequence is brought out again by an enlargement, shown in figure 1 *E*.

While a significant difference between the pattern of normal and that of rigid movement is seen in surface leads, more details of the difference in management are brought out by simultaneous leads from motor units or small groups of units with coaxial pairs of electrodes. Nine patients, 5 of whom had rigidity and tremor and 4 rigidity alone, were thus studied. As many as three pairs of coaxial needles were used in a single muscle, usually two in the protagonist and two in the antagonist. Two of the observations on patients with rigidity alone are shown in figure 2. The patients were asked to bend (fig. 2 *A*) and to stretch

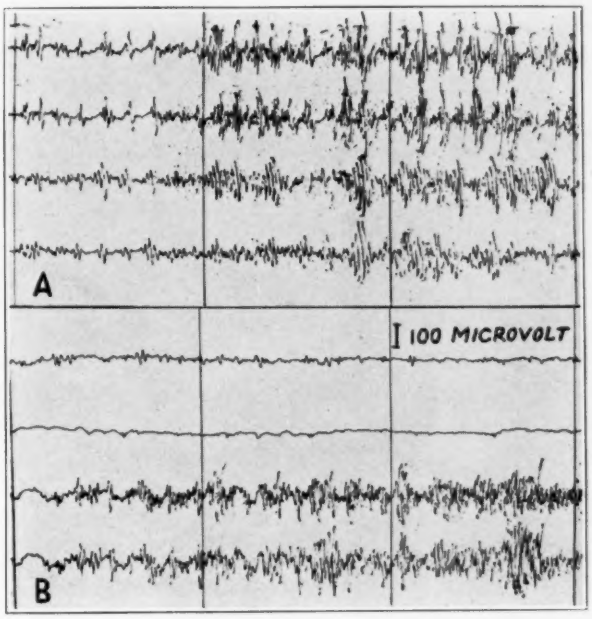


Fig. 2.—Voluntary contraction of rigid muscles in simultaneous leads of two coaxial needle electrodes each in the protagonist and the antagonist muscle. Time: one second between vertical lines. Calibration in microvolts given in *B*. Ink-writing oscillograph.

In both instances the two upper records are from the biceps unit, the two lower ones from the triceps unit: *A* (patient 32), flexion; *B* (patient 30), extension. Note that in both instances the respective antagonists are innervated with the protagonists. This is to be considered as a stretch response. The extensors in *A* respond much more strongly than the flexors in *B*. For details see text, compare also figure 4.

(fig. 2 *B*) the arm against slight resistance. In both records the two upper tracings are from the biceps muscle, the two lower ones from the triceps. There is a striking resemblance in the patterns produced by different units of one muscle. This tendency to synchronization, similar to that observed in spastic muscles under similar conditions,[3] is found in all records in varying degrees. Frequencies and

amplitudes of the spikes are high in spite of only a moderate display of strength. As in surface leads, the sequence of spikes consists of groups of bursts, roughly 6 per second, in a "staircase" pattern.

With the arrangement of electrodes used in these observations, it has been possible to study in addition the relation of opposing muscles to each other. While the arm was flexed and the pattern of a rather forceful innervation was produced in the biceps muscle, an almost equally strong discharge was seen in the triceps. Voluntary extension of the arm by powerful innervation of the triceps produced only a little activity in the biceps record. In other instances there was less difference between the influence of flexion and that of extension, respectively, on the antagonist muscles. The similarity to spasticity is obvious.

Passive Movement and "Tonus" in Rigidity.—Patients asked to carry out voluntary motion, against slight resistance or without it, experience stiffness in their limbs which they are able to overcome only with an effort in most instances. An apparently similar resistance to passive movement is a well known clinical

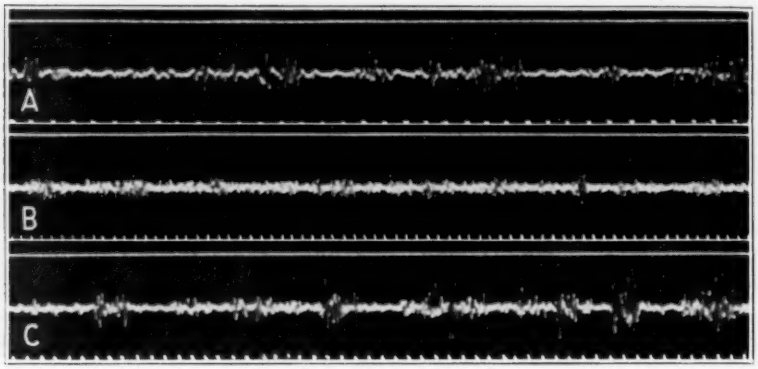


Fig. 3.—Passive movement of rigid biceps and triceps units shown in surface leads. "Cogwheel" rigidity. Time and calibration as in figure 1. Cathode ray oscillograph. *A*, patient 3; *B*, patient 4; *C*, patient 4.

sign of Parkinson's disease. It was seen that voluntary innervation produces electrical activity in antagonist muscles. This secondary activity may become almost as strong as the primary activity accompanying the active effort in the protagonist muscles.

Responses of muscles to passive movement carried out by the examiner are presented in figures 3 and 4. They were elicited from the extensor and flexor muscles of both the upper and the lower portion of the arm. Figure 3 shows tracings obtained with surface electrodes and recorded with the cathode ray oscillograph. The frequencies and amplitudes are appreciably lower than the corresponding ones in active movement, as presented in figure 1. The irregular pattern is clearly visible, especially in figure 3 *A* and *C*, which are good examples of that in "cogwheel" rigidity.

In passive, as in active, movement more detailed information is obtained from simultaneous motor unit records of opposing muscles. In figure 4 are presented three such observations from 2 patients suffering from postencephalitic rigidity without tremor. In all records, the two upper tracings are from biceps units, the

two lower ones from triceps units. The upper record (fig. 4 *A*) shows the behavior of the muscles during forceful passive flexion; the two lower records represent extension in the same manner.

By passive flexion a strong and synchronized response is produced in the triceps units in all instances, while the biceps units always show a mild and more independent activity. By passive extension a powerful and synchronous response in

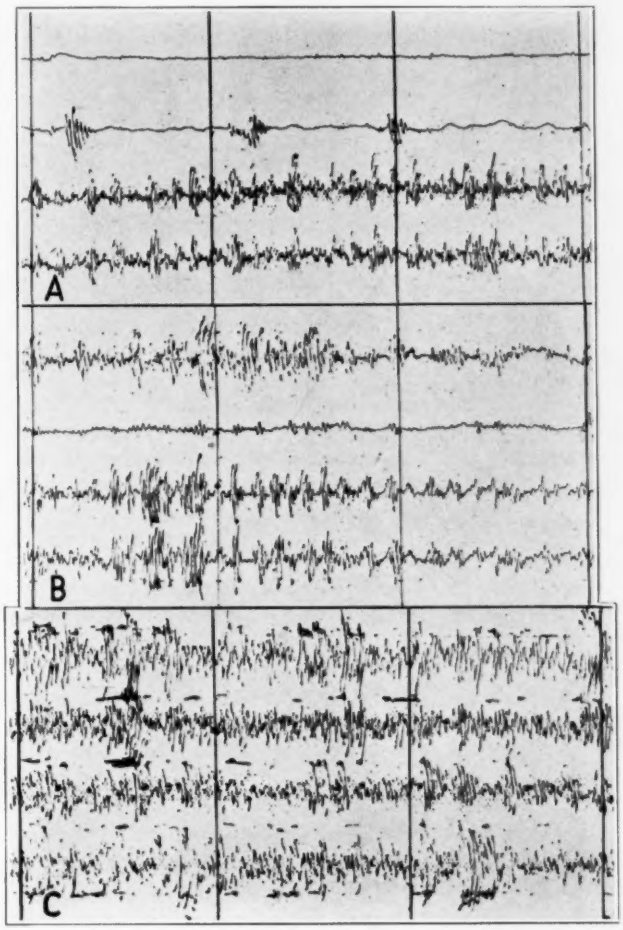


Fig. 4.—Passive movement of rigid muscles in simultaneous leads of two coaxial needle electrodes each in biceps (upper two records) and triceps (lower two records) units. Time and calibration as in figure 2. Ink-writing oscillograph. *A* (patient 32), flexion; *B* (patient 32), extension; *C* (patient 30), extension. Note the similarity between passive flexion and active extension shown in figure 2 *B*. Extensor response is always more marked than flexor response.

the biceps units is set up, as in figure 4 *C*, or less powerful and less markedly synchronized response, as in figure 4 *B*. In all instances, however, the triceps units show a high frequency and a high amplitude in patterns of almost identical aspect.

There is a good deal of similarity between records of active and those of passive movements in figures 2 and 4, except for the fact that passive extension and active flexion resemble each other and vice versa.

It should be kept in mind that by passive extension the opposing flexor muscle is being stretched and vice versa and, furthermore, that no direct stimulation is produced in a muscle when its points of insertion are brought closer together by passive movement.

It has been possible to show [3] that a spastic muscle, unless it is undergoing atrophy with fibrillation, shows no action potentials at rest, when it is not in a strained posture or subject to gravity. Thus, no trace of a basic "tonic" innervation was found in states of spasticity.

In states of pure rigidity, i. e., in the absence of tremor, there is, in contradistinction to spasticity, a constant electrical activity of low voltage traceable from all muscles, extensors as well as flexors. This activity consists of a sequence of spikes, usually of a lower frequency than that found during active or passive movement, though the frequency may become as high as in either. The voltage recorded, from 20 to 40 microvolts, is usually so low that it is seen only with high amplification. It has, therefore, been impossible to record the true range of frequencies with the cathode ray oscillograph available.

The relation of this basic sequence of impulses at rest to the electromyograms of active or passive innervation is shown in figure 5 *A*. Here activities from two units of the biceps and the triceps muscle, respectively, are recorded simultaneously just before and during onset of passive extension of the arm. The ratio of the spike amplitudes is roughly 1 : 4. A high degree of synchronization is seen in both pairs of corresponding units. A similar synchronization is seen in figure 5 *B*, recorded from another patient. In figure 5 *C* are seen tracings from a third patient who, like the other two, suffered from postencephalitic rigidity. In this instance three pairs of electrodes had been inserted in the rectus femoris muscle. The pattern and frequency of the three leads are entirely independent. The only indication of synchronization here is the fact that all three units stop discharging at the same time and start again in the same way after a pause of approximately one third of a second.

Alternating Tremor.—The electromyographic pattern of parkinsonian tremor is characteristic. It has been well established since the days of the earliest investigators.[5] A group of cathode ray–oscillographic records, selected from several hundreds, is shown in figure 6. These records were obtained with surface electrodes and with coaxial needles, in many instances from the same muscle, in successive tracings. They show a striking similarity in all instances, no matter from which muscles and by means of which electrodes they were recorded. The muscles thus studied included masseter and neck muscles and the entire extensor and flexor systems of both arms and legs. The tremors were those of rest in most cases, but in several instances tremors were recorded which, hardly visible before, were brought out by movement. Seven patients presented clinically hemiparkinsonism, but 6 of these showed electromyographic signs of presence of the tremor on the apparently uninvolved side.

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5. (*a*) Gregor, A., and Schilder, P.: Zur Methodik der Untersuchung der Muskelinnervation mit dem Saitengalvanometer, Ztschr. f. d. ges. Neurol. u. Psychiat. **15**:604, 1913. (*b*) Bornstein, A., and Saenger, A.: Untersuchungen über den Tremor und andere pathologische Bewegungsformen mit dem Saitengalvanometer, Deutsche Ztschr. f. Nervenh. **52**:1, 1914. (*c*) Cobb, S.: Electromyographic Studies of Paralysis Agitans, Arch. Neurol. & Psychiat. **8**:247 (Sept.) 1922.

The electromyogram of tremor consists of rhythmic bursts of spike potentials with electrically inactive stretches between. Each burst of spikes corresponds to one phase of the tremor movement. The free interval may last twice as long as the burst of spikes. The rate at which the tremor occurs is on the whole surprisingly regular and uniform for a given patient in different muscle groups and at different times, months apart. Only a few exceptions to this rule were seen in this series.

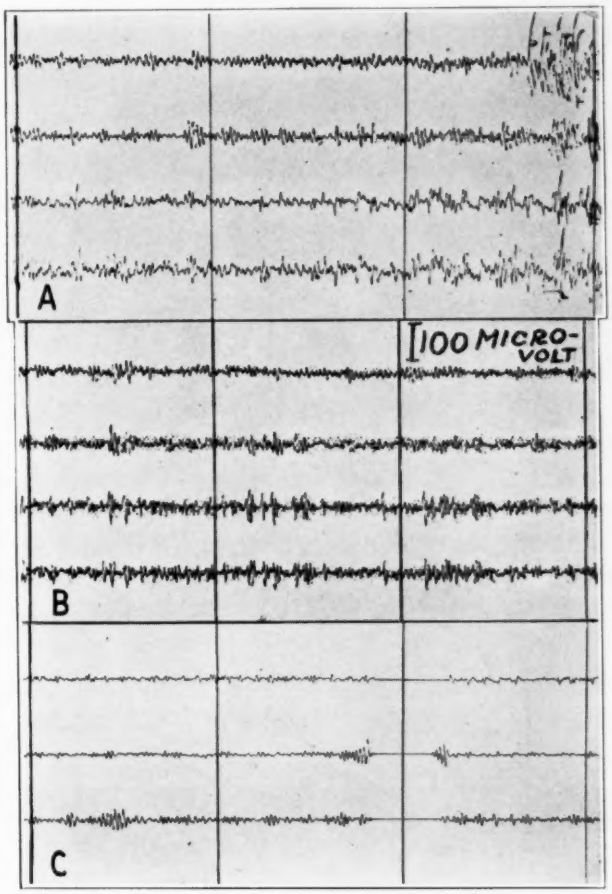


Fig. 5.—Rigid muscles at rest. *A* and *B* are from simultaneous leads of two coaxial pairs of needle electrodes each in the biceps (upper two) and the triceps (lower two) units. *A* (patient 30), onset of passive extension at the end; *B* (patient 32); *C* (patient 31), three coaxial pairs of needle electrodes in the rectus femoris muscle.

Note the more or less synchronized stream of impulses at rest, differing from that in spasticity. For details see text. Time as in figure 2. Calibration, 100 microvolts.

The average rate in this long series of cases was 5.5 per second, with a range roughly from 4 to 8 per second. The average number of spikes per burst was

15.2, with a range, again, roughly from 10 to 25. The number of spikes and the amplitudes vary in successive bursts, especially in cases of generalized tremor. The arrangement of the individual group is usually that of a "staircase" pattern.

The first two records in figure 6 *A* and *B* were taken from 2 patients, both of whom had the presenile form of Parkinson's disease. The tracings were taken with coaxial electrodes. The following two groups of two records each, *C* and *D*, and *E* and *F*, respectively, represent coaxial and surface leads from the same muscle

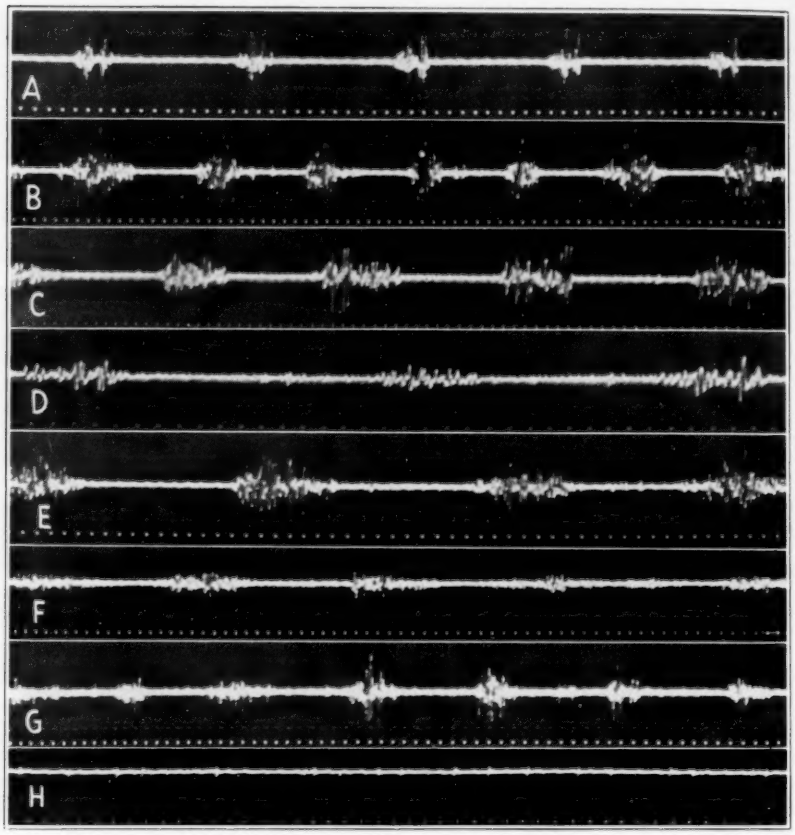


Fig. 6.—Parkinsonian tremor recorded with the cathode ray oscillograph. Time and calibration as in figure 1.

A (patient 4), coaxial electrodes in extensors of the right forearm; *B* (patient 8), coaxial electrodes in extensors of the left forearm; *C* (patient 14), coaxial electrodes in extensors of the left forearm; *D* (patient 14), surface electrodes on extensors of the left forearm; *E* (patient 7), coaxial electrodes on extensors of the left forearm; *F* (patient 7), surface electrodes on extensors of the left forearm; *G* (patient 11), coaxial electrodes on extensors of the left forearm.

Note similarity in the two types of leads. *H* was recorded from the clinically uninvolved side.

in a case of juvenile postencephalitic and a case of senile parkinsonism, respectively. The pattern and number of spikes are strikingly similar in both the surface and the

coaxial needle leads. Records *G* and *H* are coaxial needle records in another case of postencephalitic parkinsonism. In this instance only the right side was involved clinically, but unmistakable, though subliminal, activity was revealed by the needle from the depth of the corresponding muscle on the left side.

In several cases of generalized tremor simultaneous records of different muscles and their motor units were taken with the ink-writing oscillograph. In 1 of these instances a marked tremor was traced from extensor and flexor muscles of both arms and from the right masseter muscle in six leads at the same time. During part of this record the lead from the masseter muscle was replaced by one from the calf musculature of the right leg, so that a complete survey of the involved musculature was possible. It was found that in this case all the tremors

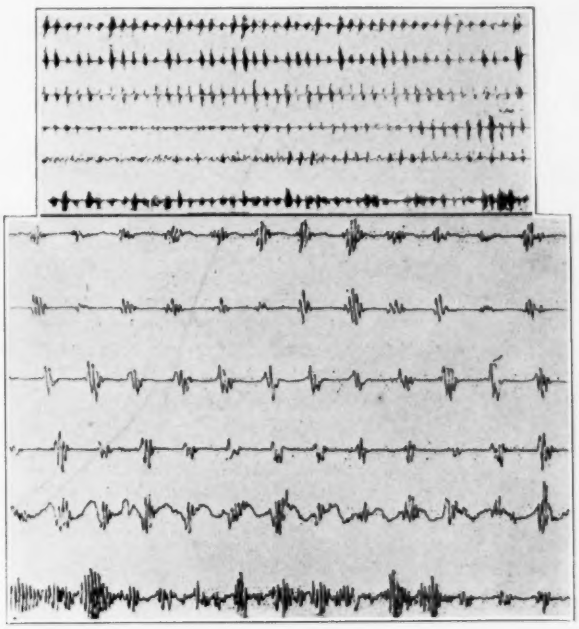


Fig. 7.—Simultaneous records from surface lead on extensors of the right forearm; surface lead on flexors of the right forearm; coaxial lead on extensors of the right forearm; surface lead on extensors of the left forearm; coaxial lead in extensor of the left forearm, and surface lead on masseter muscle on the right side. The upper part of the record was taken at slow speed; the lower part was taken at the same speed as in figure 2. Ink-writing oscillograph. For details see text.

were synchronized, allowing for alternation of flexor and extensor muscles, and that the tremor frequencies were identical everywhere. In figure 7 two parts of this experiment are reproduced. The upper record, taken at low speed, covers a run of a little over eight seconds, while the lower record, taken at high speed, shows a period of about two and one-half seconds, with greater enlargement. In the first part especially it is seen that the intensity of the tremor is shifted from one system to another, though it is always present in all regions from which

records were taken. Closer analysis of the lower record also shows how different consecutive bursts of one sequence may be. As in all ink-writer records, the frequencies of the spike potentials are not accurately reproduced, because of inertia of the magnet systems.

The relation of antagonist muscles in a case of alternating tremor is seen in figure 8. Here, one unit from an extensor and one from a flexor muscle are traced with two channels of the ink-writing oscillograph. In a number of records obtained with the cathode ray oscillograph, this relation was observed by placing surface electrodes over each of two opposing muscles. In several of these instances the bursts corresponding to the innervation of each group, respectively, are not distinctly separated from one another, but appear as one long-drawn burst of activity, leaving only a short free interval. In other cases flexor and extensor innervation are represented by clearly separated, equally distanced bursts. Both

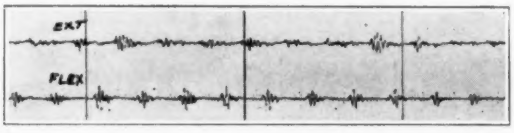


Fig. 8 (patient 29).—Alternating tremor in antagonist muscles, with one coaxial pair of electrodes in extensors and one in flexors of the forearm. Ink-writing oscillograph. Time and calibration as in figure 2.

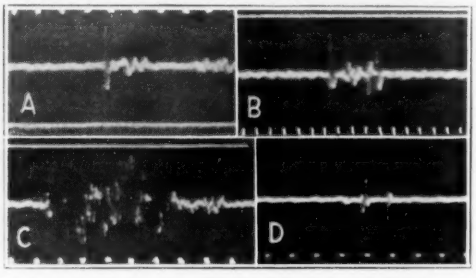


Fig. 9.—Proprioceptive reflexes in cases of paralysis agitans. Cathode ray oscillograph. The first three records were obtained with surface leads; the last was taken with coaxial needle electrodes. Time and calibration as in figure 2. *A*, patient 3; *B*, patient 1; *C*, patient 2; *D*, patient 8.

forms seem to represent subvarieties of tremor, not clearly brought out by mere clinical observation.

Reflexes.—Action potentials of proprioceptive reflexes were found to be normal (that is, to consist of essentially one spike potential) in a little more than half the patients examined. The remainder, however, showed irregular patterns of repeated spikes, sometimes with a low voltage after-discharge. No spreading of reflexes was seen, however, in cases of pure Parkinson's disease, while patients with other evidences of spasticity or with surgical interruption of the pyramidal tract did exhibit this phenomenon.

A group of abnormal reflex patterns in biceps jerks is presented in figure 9. The first three records were obtained with surface electrodes over the muscle, the

last record with a pair of coaxial needle electrodes. The first and last records (*A* and *D*) were taken from patients with senile parkinsonism with rigidity and tremor; the second and third records (*B* and *C*) from patients with the juvenile postencephalitic form.

Other Types of Tremor.—Tremor is found in a number of diseases. It may even exist without any other manifestation of nervous disease, as in alcoholism or exophthalmic goiter or after exposure to cold. Records were obtained during these experiments from a number of otherwise normal subjects who at times or to some extent always showed slight trembling of the hands. No regular action potential pattern was seen in these records of "essential" tremor.

Of greater interest within the scope of these studies is the intention tremor associated with cerebellar lesions. A number of observations in a case are presented in figure 10. They are cathode ray–oscillographic records taken with surface (*A* and *B*) and coaxial needle (*C* and *D*) electrodes, respectively, in successive leads during reasonably uniform attempts of the patient to touch the tip of his nose with his right index finger. There is no similarity between

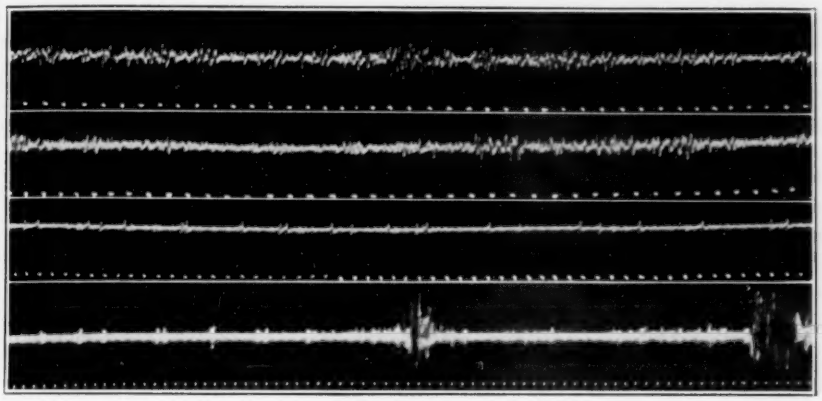


Fig. 10 (patient 38).—"Cerebellar" tremor, recorded with the cathode ray oscillograph. Time and calibration as in figure 2.

The upper two tracings were taken with surface leads; the lower two with coaxial leads. Note that there is no pattern and no similarity between the two types of records.

the records taken with the different technics, no tendency toward synchronization and even no true pattern, as with most manifestations of paralysis agitans.

Rigidity of Nonparkinsonian Origin.—A peculiar form of muscular rigidity was studied in 1 instance. The patient, a man aged 69, had a history of tabes dorsalis, which had been treated adequately and had become inactive fifteen years prior to entry. He began drinking heavily. One month prior to entry he became progressively weaker and a few days before he became suddenly rigid all over and stuporous. Examination showed extreme rigidity. Tendon reflexes were not obtained; the pupils were large and reacted sluggishly. There was a Babinski response bilaterally. Electromyographic studies showed constant activity of low voltage when the patient was at "rest," which was increased by passive movements in attempts to overcome the muscular stiffness. This activity, which at times was highly synchronized, at other times less so, closely resembled that seen

in postencephalitic rigidity without tremor, as shown in figure 5. The tentative clinical diagnosis of Wernicke's polioencephalitis haemorrhagica superior and tabes dorsalis (asymptomatic) was made. The patient's condition remained essentially unchanged until his death about two months after the onset of rigidity.

Dr. Leo Alexander's gross description of the brain follows: "There were generalized atrophy of the cortex and basal ganglia and advanced granular ependymitis, apparently older and probably related to syphilis. The more recent involvement consisted of widespread disease of the central and convolutional white matter of the brain, probably vascular with elements of arteriosclerotic and syphilitic vascular disease. The dentate nucleus and brachium conjunctivum on both sides showed gray-brownish discoloration of recent vascular origin. The tabetic changes in the posterior columns presumably had acted as partial deafferentation."

It is probably justifiable, therefore, to consider the physiologic state of this patient as one of decerebration and decerebellation. It is interesting to note that the partial destruction of the posterior columns had no influence on the rigidity, as in Sherrington's [6] experiment.

Electromyograms Following Drug and Surgical Therapy.—No appreciable difference was seen between the electromyograms of patients who had been treated, as a rule for many years, with drugs of the atropine series and those of the few patients who never had had any treatment. While the tremor occurred, even in patients considered as "clinically improved," the tremor pattern came out clearly and with the same range of frequency and amplitude of the spikes. It is necessary to keep in mind that normally a variation exists, especially with generalized tremor, as figures 6 and 7 show.

It is possible, however, in some cases to reduce tremor considerably and consistently, or even to abolish it for short periods, up to twenty-four hours, by intravenous injection of curare. Several samples of this drug were tried at different times. Not all of them were effective. Some produced general effects of a highly toxic nature while, or even before, the desired effect was in evidence. Others had only equivocal effects. Several striking observations, however, were made with a sample of curare (Merck) prepared and standardized in our own laboratory.

One of these observations is shown in figure 11. In this experiment surface electrodes were used in all leads. They were so placed that one was on the extensor and one on the flexor group of the left forearm. This is one of the instances in which extensor and flexor bursts were clearly spaced and also one in which effort had the effect of increasing the tremor. Figure 11 *A* and *B* show tremor and strong voluntary effort before injection of curare. The third record (fig. 11 *C*) shows a suggestion of tremor action potentials persisting twenty-four hours after a successful injection of a large but subtoxic dose. The last two records show the differential effect of a somewhat smaller dose of the same preparation on a different occasion, ten minutes after the injection. While tremor at rest is completely abolished and only small traces of the electrical pattern are visible on the record (fig. 11 *B*), the amplitude and grouping of the spikes produced by voluntary movement are unchanged. It should be noted that effort restores the tremor to a certain degree. Judging from our own experiences, therefore, treatment of paralysis agitans with curare has not yet reached a practical stage.

6. Sherrington, C. S., cited by Fulton.[15a]

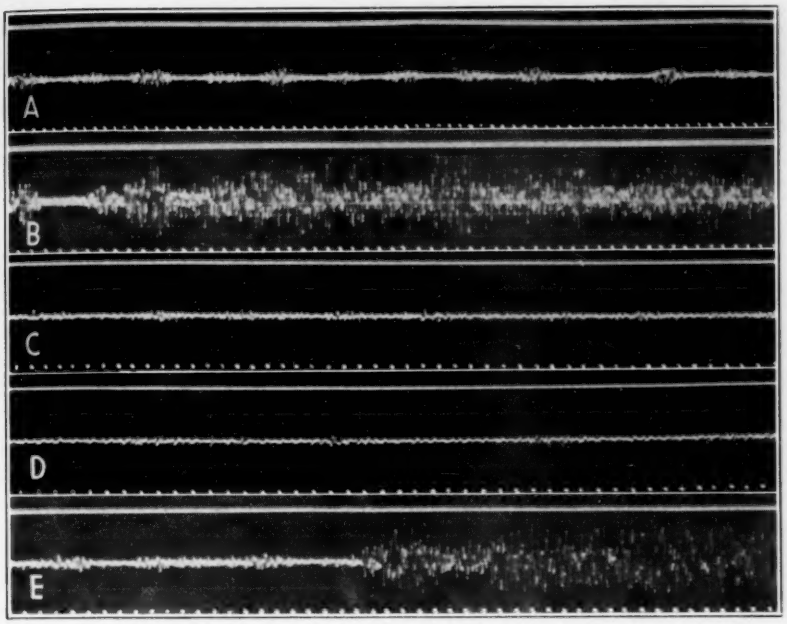


Fig. 11 (patient 5).—Effect of curare on tremor and voluntary movement in a case of paralysis agitans. Surface electrodes, one on flexors and one on extensors of the forearm. Cathode ray oscillograph. Time and calibration as in figure 2. Note the separate bursts for flexion and extension in the tremor leads.

A, tremor before injection; *B*, voluntary grip before injection; *C*, residual tremor twenty-four hours after injection of a large amount of curare; *D*, residual tremor ten minutes after another injection of a smaller amount, and *E*, voluntary grip recorded at the same time that the tracing shown in *D* was taken.

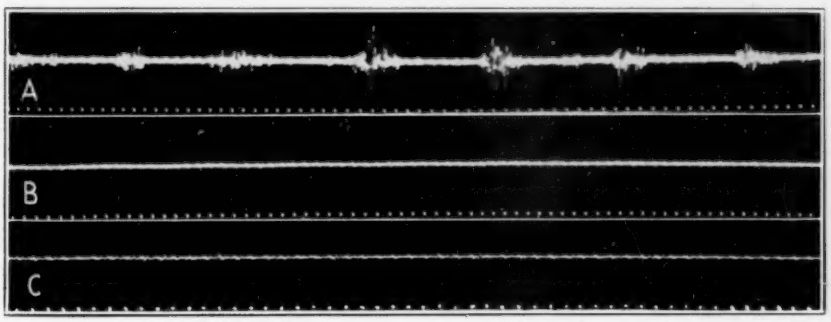


Fig. 12 (patient 11).—Effect of section of the pyramidal tract on parkinsonian tremor. Cathode ray oscillograph. Time and calibration as in figure 2. Coaxial needle leads from extensors of the right forearm in all three records. *A*, before operation; *B*, ten days after operation with the patient at rest; *C*, subliminal tremor pattern produced by elevation of the extended arm (time as in *B*).

A much more permanent method of abolishing tremor has been used in several instances by one of us (T. J. P.).[7] It consists in section of the lateral pyramidal tract at an upper cervical level. In 6 cases of unilateral tremor operation has thus been performed, with surprisingly good results in 3 instances in which complete section was performed. Partial section was followed by partial relief in 2 instances and by failure in 1.

In figure 12 electromyograms in a case of parkinsonism are shown. All three records were obtained with coaxial needle electrodes. The first picture is that of the arm tremor before the operation. The second shows complete abolition of all traces of the tremor several weeks after operation, while the third shows a faint, subliminal tremor pattern, without noticeable tremor during strong effort. The patient was able to move the arm, hand and fingers, even in fine movements. Her strength was only moderate, but she was not paralyzed. She has since shown several signs of spasticity.

COMMENT

Two abnormal motor phenomena, tremor and rigidity, linked together in a clinical entity, Parkinson's disease, have been studied in this investigation. A survey has been made of the electromyographic patterns produced by these phenomena and of those of other forms of motor performance of patients suffering from the disease.

From the beginning certain similarities between tremor and rigidity, on the one hand, and clonus and spasticity, on the other have been pointed out. It has been stated that patients in either group of conditions may suffer from a similar motor loss as far as practical performance is concerned.

In Parkinson's disease voluntary effort may vary over a wide range. In some instances motor performance and electrical pattern are almost normal. In others a complete dissociation is seen by which the movement is changed to a jerky staccato. Strength may vary in a similar way. Fatigue is a common symptom. Amplitudes and frequencies are, however, almost invariably high, unlike the situation in spasticity,[3] and there is reason to believe that muscular strength goes parallel with these two factors.

Simultaneous motor unit records show a consistent tendency toward synchronization in all forms of parkinsonian activity. In this respect, Parkinson's disease is similar to spasticity,[3] and motor unit management in this condition is unlike that in normal movement.[2] Furthermore, simultaneous records of opposing muscles show that again, like innervation in spasticity and unlike normal muscle management, antagonist muscles are activited as a result of volitional movement. The nature of this practically simultaneous innervation is made clearer by observation of the results of passive movement. The antagonist activity is thus shown to be of reflex nature. This reflex innervation of opposing

7. Putnam, T. J.: Relief of Unilateral Paralysis Agitans by Section of the Pyramidal Tract, Arch. Neurol. & Psychiat. **40**:1049 (Nov.) 1938.

muscles seems a reasonable explanation for the stiffness and at least part of the weakness of volitional movement, while the synchronicity of motor unit discharge may explain the higher degree of fatigue.

A synchronized basic stream of impulses of low voltage was found consistently in all cases of rigidity without tremor. In this respect it has been impossible to confirm the observations of Altenburger,[8] who saw no action potentials during rest in cases of rigidity in string galvanometer records and came to the conclusion that rigidity is a condition of the contractile substance of the muscle fiber. It is necessary to keep in mind that the basic "tonic" activity in the rigid muscles has a voltage range between 20 and 40 microvolts, which is beyond the range of the string galvanometer. It is justifiable, therefore, to conclude that rigidity consists of two components: a basic underlying constant innervation, probably of central origin, by which it is distinguishable from spasticity,[3] and a reflex component, which has great similarity to spasticity.

Suggestive evidence for the postural reflex nature of at least part of the parkinsonian rigidity was produced by Walshe,[9] who abolished it temporarily by intramuscular injection of procaine hydrochloride. The amount injected was thought to be sufficient to "deafferent" the muscles without impairment of motor power. Tremor was apparently not influenced by this procedure. Pollock and Davis [10] resected all the posterior roots between the fourth cervical and the fourth dorsal segment for complete deafferentation of a rigid arm. The result was flaccidity to passive movement in most muscles, with the exception of the flexors, and a contracture in flexion followed. Tremor was not abolished, but its pattern was considerably changed. It was no longer regular but varied in rate, which was at times as low as 2 per second and at other times fast. Its amplitude was also changed. Still less clear is the result of an operation reported by Puusepp,[11] who in 1 case made an incision of about 4 mm. in Burdach's column at the fifth cervical level, after which rigidity was apparently reduced while tremor was only temporarily diminished and returned later. There is good experimental [6] and, on the other hand, clinical (see page 716) evidence to support the conception that decerebrate rigidity is not abolished by section of the posterior column.

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8. Altenburger, H.: Spasmus und Rigor: Eine vergleichende physiologische Studie, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:402, 1937.

9. Walshe, F. M. R.: Observations on the Nature of the Muscular Rigidity of Paralysis Agitans and on Its Relationship to Tremor, Brain **47**:154, 1924.

10. Pollock, L. J., and Davis, L.: Muscle Tone in Parkinsonian States, Arch. Neurol. & Psychiat. **23**:301 (Feb.) 1930.

11. Puusepp, L.: Cordotomia Posterior Lateralis (Fasc. Burdachi) on Account of Trembling and Hypertonia of the Muscles in the Hand, Folia neuropath. estoniana **10**:62, 1930.

The "tonic after-discharge" of tendon reflexes described by Foerster and Altenburger,[12] which was seen in a number of instances in these experiments, belongs to the same group of phenomena. It should be pointed out, however, that spreading of reflexes was not observed in cases of pure Parkinson's disease, while it has been shown to be rather typical for spasticity. It was attributed in spastic conditions to release of intrinsic cord systems following lesions of the pyramidal tract.[3]

Rigidity resembling that of "decerebration" in animal experiments was found in 1 clinical case. Autopsy showed decortication and partial bilateral destruction of the basal nuclei, the cornu ammonis, the dentate nucleus, the brachium conjunctivum and the posterior column. Here the electromyographic pattern was similar to that in cases of parkinsonian rigidity. A number of authors [13] have described the electromyographic pattern of experimental "decerebrate rigidity," and it is interesting to note that this state is also apparently maintained by a constant influx of electrical impulses. Walshe [14] expressed the belief that spasticity is a manifestation of decerebrate rigidity, but rejected the idea that parkinsonian and decerebrate rigidity are related. Elsewhere, however, he [9] considered strongly the possibility that parkinsonian rigidity is "a true proprioceptive reflex."

The recent work of Fulton and his associates [15] has pointed to interesting relations between rigidity and spasticity from another point of view, and will be commented on later.

A tendency to synchronization of motor units in pattern, frequency and rate similar to that in clonus is characteristic of parkinsonian tremor, but not of cerebellar tremor. Clonus has been shown to be an intrinsic cord or segmental mechanism. The phenomenologic similarity between clonus and tremor, as an alternating innervation of antagonists, has been pointed out by Kinnier Wilson,[16] who called both of them "physiological states of low order" and expressed the belief that the similarity of rates "cannot be pure coincidence, even though the anatomical cause of their respective releases be structurally different in each." Cobb [5e] and

12. Foerster, O., and Altenburger, H.: Die Dehnungs- und Annäherungsreflexe beim Pallidumsyndrom, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:588, 1934.

13. Dusser de Barenne, J. G., and Brevée, J. F. G.: The Interpretation of the Electromyogram of Striated Muscle During Contractions Set up by Central Nervous Excitation, J. Physiol. **61**:81, 1926. Bremer, F., and Titeca, J.: Atonie curarique et inhibition de Wedensky, Arch. internat. de physiol. **42**:223, 1935.

14. Walshe, F. M. R.: The Decerebrate Rigidity of Sherrington in Man, Arch. Neurol. & Psychiat. **10**:1 (July) 1923.

15. Fulton, J. F.: (*a*) Physiology of the Nervous System, New York, Oxford University Press, 1938; (*b*) Spasticity and the Frontal Lobes, New England J. Med. **217**:1017, 1937.

16. Wilson, S. A. K.: Modern Problems in Neurology, London, Edward Arnold & Co., 1928, chap. 6.

Lindsley [17] pointed out the similarity of the electrical patterns of the two phenomena as seen in records from single leads.

The rate of tremor is usually rather constant and uniform for a given patient. In several instances of generalized tremor we found a surprisingly exact synchronization along the whole neuraxis, from the masseter to the calf musculature. This constancy of rate is in accord with the observations of most authors. Cobb [5c] found rates constant over periods of many months. Deviations, however, were noted in a few cases of this series. Schwab and Cobb [18] recently found a higher incidence of deviations, but still isochronism, in the majority of their cases. Herz,[19] in an analysis of slow motion pictures, observed occasional differences in rate of tremor between the fingers in 2 of 5 cases of "pill-rolling" tremor.

It is more significant, we believe, that in most instances the rate of tremor is uniform than that there are exceptions, which are usually of a minor degree. This points to the release of a true physiologic mechanism rather than to stimulation from an irritating lesion as the origin of tremor. Any attempt to understand this mechanism should take into account the regularity of the rhythm, the synchronous timing in transmission over pathways varying considerably in length and the peculiar shift in intensity of the tremor from one group of muscles to another. The relation of tremor to rigidity should also be considered.

At first sight it seems unlikely that impulses originating in a focus in the midbrain and discharged over long tracts, such as the subcorticospinal, could reach muscles as far separated as the masseter and the calf muscles practically simultaneously, as they are found to do. The speed of transmission of impulses depends on the size of the conducting fiber.[20] The maximal speed of conduction for the somatic myelinated motor fibers has been found to be between 90 and 30 meters per second, and fibers to small muscles may conduct rates as low as 15 meters per second. The distribution in size varies little in different motor roots. Little is known about the conduction in central structures, but it is justifiable to assume that similar roles are valid here.[21] The high speed at which motor impulses are conducted at maximum would cause only an inconsiderable

17. Lindsley, D. B.: Electromyographic Studies of Neuromuscular Disorders, Arch. Neurol. & Psychiat. **36**:128 (July) 1936.

18. Schwab, R. S., and Cobb, S.: Simultaneous Electromyograms and Electroencephalograms in Paralysis Agitans, J. Neurophysiol. **2**:36, 1939.

19. Herz, E.: Die amyostatischen Unruheerscheinungen: Klinisch-kinematographische Analyse ihrer Kennzeichen und Begleiterscheinungen, J. f. Psychol. u. Neurol. **43**:3, 1931.

20. Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activities, Philadelphia, University of Pennsylvania Press, 1937.

21. Häggquist, T.: Faseranatomische Studien über die Pyramidenbahn, Acta psychiat. et neurol. **12**:457, 1937.

difference in time of arrival for impulses flashed at equal speed to the jaw and to the calf muscles, and in consideration of the possibility that somewhat smaller fibers conduct motor impulses to the jaw, this difference would become even less marked. Simultaneous records at high speed would be necessary to decide this point definitely. At the same time, the perfect alternation of antagonists so closely resembling clonus is not easily understood.

A more serious difficulty is that of unequivocally attributing the transmission of impulses arising in the midbrain to any known pathway in the central nervous system. Unlike athetosis, alternating tremor is neither improved nor aggravated by extensive sections of the anterolateral extrapyramidal tracts in the cord.[22]

It seems more likely, for several reasons, that the tremor impulses are conducted along the pyramidal tracts. Parkinson [23] saw tremor disappear after hemiplegia and return as the paralysis receded. Bucy and Case [24] abolished unilateral tremor in 1 instance by excision of the motor and the premotor cortex (areas 4 and 6 a). Klemme [25] extirpated nonexcitable cortex from the frontal lobe alone and alleviated the tremor. We have not been able to confirm this observation, but have seen relief from removal of area 6 a alone in 2 cases. After complete section of the lateral pyramidal tract in the cord, tremor disappeared largely or entirely in 3 cases.[7] In order to understand how tremor impulses were transmitted along the pyramidal tracts, it would become necessary to assume the existence of a recurrent pathway from the basal ganglia to the cortex. To explain its rhythmicity a number of auxiliary hypotheses would have to be made.

An old observation, dating back to Parkinson's time, is that voluntary effort, presumably transmitted by the pyramidal tracts, will also stop tremor and even decrease rigidity for a short time in some cases. In others volitional effort increases both. Thus the pyramidal tracts show an almost ambivalent function in regard to tremor.

The part played by various portions of the motor cortex and their long projections in mediating other types of abnormal movement is also somewhat obscure. Relief of athetosis by resection of the anterior portion of the corresponding motor cortex (apparently Brodmann's area 6 a) was

22. Putnam, T. J.: Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Psychiat. **39**:258 (Feb.) 1938.

23. Parkinson, J.: An Essay on the Shaking Palsy, London, Sherwood, Neely & Jones, 1817; reprinted in Medical Classics, Baltimore, Williams & Wilkins Company, 1938, vol. 2, p. 957.

24. Bucy, P. C., and Case, T. C.: Tremor: Physiologic Mechanism and Abolition by Surgical Means, Arch. Neurol. & Psychiat. **41**:721 (April) 1939.

25. Klemme, R. M.: Personal communication to the authors.

first reported many years ago by Horsley.[26] His results have been confirmed by several surgeons since, but failures have also occurred. There is good reason for believing that the fundamental physiologic mechanism producing athetosis is substantially different from that producing tremor.

The normal electrical rhythm of the motor area of the cortex has been found to be undisturbed in cases of severe parkinsonian tremor,[18] and this might indicate that tremor impulses do not originate in the motor cells of area 4 or area 6 a, both of which send their long projections down to the spinal segments without any interruption or connection.[27] It has to be admitted, however, that the electrical rhythms of the cortex are not yet fully understood and that normal voluntary innervation of muscles has no apparent correlation in the electroencephalogram.[28]

Furthermore, the management of motor units in tremor as well as in rigidity is different from the characteristic synchronous discharge which is seen in normal innervation,[2] for which intactness of the pyramidal tract appears to be essential. In paralysis agitans the discharge is of the more simplified synchronous type, similar to that seen in spastic hemiplegia or after transection of the cord.

It is therefore impossible with the evidence at present available to state whether the impulses for tremor are conducted along the corticospinal projections of areas 4 and 6 a or whether they may be conducted by other paths. It is safe to say, however, that tremor is possible only as long as the pyramidal tracts are substantially intact.

Walshe [9] has attempted to disprove Hughlings Jackson's well known conception of the relation of tremor and rigidity and has shown evidence that the two phenomena are entirely independent. The observations reported here show, however, that they have several features in common. One, which has been repeatedly pointed out, is the management of muscles by synchronous motor unit discharge. Another is that both tremor and rigidity show components of two different activities. In rigidity a basic innervation at rest is seen, to which a component in the nature of a stretch reflex is added as soon as active or passive movement begins. In alternating tremor a type of innervation is revealed which is indistinguishable as far as electrical impulses are concerned from the one by which opposing muscles are operated in clonus, which is presumably a segmental mechanism of the nature of an alternating stretch reflex. There is an obvious difference, however, in that clonus needs

26. Horsley, V.: The Function of the So-Called Motor Area of the Brain, Brit. M. J. **2**:125, 1909.

27. Hoff, E. C., and Hoff, H. E.: Spinal Terminations of the Projection Fibers from the Motor Cortex of Primates, Brain **57**:454, 1934.

28. Adrian, E. D., and Matthews, B. H. C.: The Berger Rhythm: Potential Changes from the Occipital Lobes in Man, Brain **57**:355, 1934.

an external stimulus to set it off, while tremor starts, stops and is shifted, for instance from the extensor-flexor to the pronator-supinator pair in a forearm, by what might be called an internal stimulus.

In the presence of tremor the basic innervation of rigidity is usually not seen in the record. Between the action potential groups of the tremor phases, electrical inactivity is the rule even at high amplification. There are, however, records of tremor in which this basic activity is present, and, furthermore, the different bursts of tremor have often a tendency to become longer, partly filling in the interval between them, so that it seems not infrequently as if tremor could be "run together."

It might thus be assumed that a source of internal stimulation is released and is responded to constantly in a mild degree as "basic" rigidity in cases of the pure form or rhythmically as tremor. Both do coexist often, but tremor tends to blot out the weaker form of basic rigidity, except when the latter is searched for by special means.

The "internal" factor might be considered to "release" and utilize preformed spinal mechanisms, such as the "stretch" response and "clonus," one at a time or the two together to a varying degree, and also the synchronous motor unit management in voluntary movement, such as that of weak hemiparetic muscles in spasticity.[3] Generalized tremor might then be considered as a function of Wilson's [16] "old" motor system, released as a whole or in large part and acting in response to regular internal stimuli from above. Spasticity, in contrast, may occur when segmental mechanisms alone are released. The observation of Pollock and Davis [10] that after deafferentation tremor lost its regularity in alternation and rhythm seems to suggest that the rate of tremor is dependent on a segmental reflex mechanism.

In decerebrate rigidity a "basic" stream of action potentials was found by Dusser de Barenne and Brevée [13] after section and after cocainization of the posterior horns. A similar observation was made on the patient with rigidity in the presence of atrophy of the posterior columns already described. This seems to indicate that "basic" innervation is not of reflex nature. It remains even after the major portion of rigidity, namely, that part which is postural reflex, is abolished by root section. The contracture resulting from section of posterior roots for rigidity in the cases of Pollock and Davis [10] and of Foerster and Gagel [29] might be interpreted as further evidence pointing in the same direction.

SUMMARY

Electrical records have been taken by means of single or multiple surface or coaxial leads from the muscles in a variety of cases of tremor and rigidity.

29. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1, 1932.

In paralysis agitans voluntary movements produce electrical records characterized by abnormal synchronization of the motor units innervated. A similar synchronization has also been reported in cases of spasticity.

The state of parkinsonian rigidity is characterized by a continuous slight innervation of the rigid muscles, even when the limb is placed in its most relaxed position. No such constant innervation has been observed in cases of spasticity.

Stretching of a rigid muscle, by means of either active or passive movement, produces a marked increase in this innervation. In this respect, rigidity resembles spasticity. Deep reflexes in cases of rigidity may or may not take a "spastic" form, but they do not spread to other muscles, as in true spasticity.

A characteristic parkinsonian tremor consists of bursts of innervation, affecting alternately protagonists and antagonists, at an average rate of 5.5 per second. The rate is surprisingly constant over long periods and in all the muscles affected. No such constancy is seen in "cerebellar" and in "essential" tremors.

The bursts of innervation of tremor affect all activated motor units synchronously. There is usually quiescence of antagonists during them.

The electrical activity characteristic of tremor is abolished temporarily by injection of curare under favorable circumstances. It is greatly diminished, apparently permanently, by section of the pyramidal tract in the lateral column of the spinal cord and by resection of the cortical area 6 a.

Possible explanations for these phenomena are discussed.

INFLUENCE OF INSULIN AND OF STIMULATION OF THE SYMPATHETIC NERVOUS SYSTEM ON THE BLOOD

STUDY OF THE SUGAR CONTENT, CARBON DIOXIDE TENSION AND p_H

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In a number of investigations, it has been shown by Gellhorn and his collaborators [1] that anoxia and hypoglycemia affect the central nervous system in a similar manner and bring about potentiating effects on this system if the two procedures are combined. It was concluded that both anoxia and hypoglycemia decrease the oxidative state in the brain and that this, in turn, leads to stimulation of the sympathetic centers.

Himwich and his associates [2] recently called attention to effects on the vagus nerve during insulin hypoglycemia and anoxia, and concluded from these observations that the major effect of insulin hypoglycemia is increased parasympathetic activity. For this reason, it seemed to us of interest to find additional criteria for the nature of the effects produced by insulin hypoglycemia.

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1. (*a*) Gellhorn, E.; Ingraham, R. C., and Moldavsky, L.: The Influence of Hypoglycemia on the Sensitivity of the Central Nervous System to Oxygen Want, J. Neurophysiol. **1**:301, 1938; (*b*) Effects of Hypoglycemia and Anoxia on the Central Nervous System: Basis for Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125 (July) 1938. (*c*) Ingraham, R. C., and Gellhorn, E.: Role of Adrenals in Blood Pressure Reaction to Anoxia During Insulin Hypoglycemia, Proc. Soc. Exper. Biol. & Med. **40**:315, 1939. (*d*) Kraines, S. H., and Gellhorn, E.: The Effects of Insulin Hypoglycemia on the Blood Pressure Response to Oxygen Deficiency in Man, Am. J. Psychiat. **95**:5, 1939. (*e*) Yesinick, L., and Gellhorn, E.: Studies of Increased Intracranial Pressure and Its Effects During Anoxia and Hypoglycemia, Am. J. Physiol. **128**:185, 1939.

2. Himwich, H. E.; Martin, S. J.; Alexander, F. A. D., and Fazekas, J. F.: Electrocardiographic Changes During Hypoglycemia and Anoxia, Endocrinology **24**:536, 1939.

It is well known that in conditions of excitement, in addition to signs of general increased activity and discharge of epinephrine (increased heart rate and blood pressure, decreased clotting time, increased blood sugar),[3] the respiratory rate is increased. Since similar effects are observed in anoxia and on stimulation of those parts of the hypothalamus from which sympathetic effects are elicited, it was thought of interest (1) to determine whether in the unanesthetized dog excitement induced physiologically or pharmacologically leads to significant changes in respiration, evidenced by alteration in the carbon dioxide tension of the arterial blood, and, if this is the case, to ascertain its correlation with the sugar content of the blood and (2) to determine whether in man and in animals similar changes may be observed during insulin hypoglycemia, a finding which may indicate that a sympathetic reaction is evoked.

Therefore a series of experiments was carried out on man and dogs in which the effects of insulin hypoglycemia were compared with those obtained when the sympathetic centers were stimulated. For such stimulation, excitation and the injection of metrazol and of relatively large quantities of epinephrine were the methods chosen. In addition to the alterations in blood sugar, the effects of these various procedures on the carbon dioxide tension of the alveolar air and of the arterial blood and on the p_H of the arterial blood were determined.

METHODS

Twenty-four experiments were carried out on male schizophrenic patients, who were given injections of insulin.[4] The carbon dioxide content of the alveolar air was determined, with the Henderson-Haggard[5] method, at various levels of the blood sugar. Eight experiments were carried out with insulin hypoglycemia in dogs which were either narcotized with morphine or used without narcosis. In the latter case, arterial blood was obtained from the left ventricle. The dogs were trained to remain quiet during this procedure. Furthermore, 10 dogs were used in which the influence of excitation and pain on the sugar, the p_H and the carbon dioxide tension of the blood was studied. Finally, 7 dogs were given injections of metrazol in subconvulsive and convulsive concentrations, and 6 other dogs received epinephrine subcutaneously. The sugar was determined by the Somogyi modification of the Shaffer-Hartman method. The carbon dioxide content of the arterial blood was determined by the Van Slyke manometric method. The p_H of the blood was determined potentiometrically with the quinhydrone electrode, and the carbon dioxide tension was calculated according to the method of Peters and Van Slyke.[6]

3. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton and Company, 1929.

4. The insulin was supplied by Eli Lilly and Co., Indianapolis.

5. Henderson, Y., and Haggard, H. W.: The Circulation and Its Measurement, Am. J. Physiol. **73**:193, 1925.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, William & Wilkins Company, 1932, vol. 2.

RESULTS

Effect of Insulin on the Sugar, p_H and Carbon Dioxide Tension of Arterial Blood.—A series of experiments was carried out on psychotic patients and on animals in order to determine the relationship between hypoglycemia and carbon dioxide tension of the alveolar air or arterial blood. It was found that, in general, with a fall in the blood sugar the carbon dioxide tension of the alveolar air fell also. It was noted, however, that the two processes did not run parallel, as the fall of blood sugar from the control level of about 80 or 100 mg. per hundred cubic centimeters to 50 or 55 mg. was not accompanied by any significant change in carbon dioxide tension. If, however, the blood sugar dropped below this value it was accompanied by a distinct fall of the carbon dioxide tension of the alveolar air.[7]

TABLE 1.—*Influence of Administration of Sucrose on Blood Sugar and Carbon Dioxide Concentration of Alveolar Air*

	Before Administration of Sucrose		After Administration of Sucrose	
No.	Blood Sugar, Mg. per 100 Cc.	Percentage of Carbon Dioxide in Alveolar Air	Blood Sugar, Mg. per 100 Cc.	Percentage of Carbon Dioxide in Alveolar Air
1	38.1	4.98	95.3	5.09
2	46.5	4.78	63.5	4.92
3	47.5	4.19	109.0	5.07
4	48.5	4.95	133.0	4.98
5	35.2	4.66	53.0	4.81
6	57.3	3.61	98.2	4.10
7	46.0	3.52	117.0	4.44

If the fall of the blood sugar below a critical level is accompanied by a fall of the carbon dioxide tension of the alveolar air, it is to be expected that restoration of the blood sugar on the administration of sucrose by stomach tube would be accompanied by a rise in the carbon dioxide tension. Table 1 shows that that, in fact, is the case.

The statement that low blood sugar is associated with a decrease in the carbon dioxide tension of the alveolar air needs to be modified when the patient is in a state of coma. The blood sugar then remained low, or fell even lower, but the carbon dioxide tension of the alveolar air rose. Six observations of this kind are embodied in table 2. These experiments seem to indicate that hypoglycemia stimulates respiration, provided that the excitability of the respiratory center is not altered significantly. If, however, its excitability is greatly lowered, as in deep coma, even a further fall in blood sugar may be accompanied by a decrease in respiratory volume, as shown by a rise in the carbon dioxide tension of the alveolar air.

7. Gellhorn,[1b] table 2.

When the fact is taken into account that a fall in blood sugar is accompanied by lowering of the carbon dioxide tension of alveolar air but that in coma there is an opposite effect, it is clear, since the onset of the coma is not easily determined, that in some cases the changes in carbon dioxide tension of alveolar air may not be great in spite of a considerable decrease in blood sugar.

TABLE 2.—*Relation of Carbon Dioxide Tension of Alveolar Air and Blood Sugar in Hypoglycemia Coma*

	Before Coma		In Coma	
No.	Blood Sugar, Mg. per 100 Cc.	Percentage of Carbon Dioxide in Alveolar Air	Blood Sugar, Mg. per 100 Cc.	Percentage of Carbon Dioxide in Alveolar Air
1	41.2	4.88	47.2	5.2
2	45.1	4.47	36.8	5.14
3	35.3	2.34	17.2	2.90
4	34.8	3.72	27.0	4.23
5	37.8	4.87	34.3	5.22
6	35.2	4.66	28.0	5.03

TABLE 3.—*Influence of Insulin Hypoglycemia on the Sugar, Carbon Dioxide Tension and p_H of Arterial Blood*

Dog no. 1: weight 15.5 Kg.; fasted 24 hours
10:10 a. m.: Blood sugar, 79.6 mg. per 100 cc.; carbon dioxide, 25.7 mm.; p_H, 7.45
10:17–10:20 a. m.: 5 units of insulin per Kg. intravenously
5 units of insulin per Kg. intramuscularly
11:40 a. m.: Blood sugar, 19.1 mg. per 100 cc.; carbon dioxide, 20.8 mm.; p_H, 7.40
11:55 a. m. 80 Gm. dextrose in 300 cc. of water by stomach tube
The dog, which was very unstable on its feet prior to the injection of dextrose, showed normal muscular coordination and behavior almost immediately after the administration of dextrose
12:35 p. m.: Blood sugar, 70.9 mg. per 100 cc.; carbon dioxide, 19.0 mm.; p_H, 7.48
1:40 p. m.: Blood sugar, 103.2 mg. per 100 cc.; carbon dioxide, 23.5 mm.; p_H, 7.44

Dog no. 2; weight 18 Kg.; fasted 24 hours
10:34 a. m.: Blood sugar, 94.6 mg. per 100 cc.; carbon dioxide, 36.7 mm.; p_H, 7.34
10:37 a. m.: 5 units of insulin per Kg. injected intramuscularly
10.43 a. m.: 5 units of insulin per Kg. injected intravenously
12:50 p. m.: Blood sugar, 41.9 mg. per 100 cc.; carbon dioxide, 31.3 mm.; p_H, 7.29
12:55 p. m.: 2 units of insulin per Kg. injected intravenously
2:20 p. m.: Blood sugar, 32.2 mg. per 100 cc.; carbon dioxide, 22.2 mm.; p_H, 7.39
2:30 p. m.: 20 cc. of 20% dextrose intravenously
3:30 p. m.: Blood sugar, 53.7 mg. per 100 cc.; carbon dioxide, 24.3 mm.; p_H, 7.39

In order to investigate the relationship between the blood sugar and the carbon dioxide tension of alveolar air under simpler conditions, experiments were carried out on unnarcotized trained dogs in which blood from the left ventricle was analyzed for its carbon dioxide tension, sugar content and p_H. Typical experiments are recorded in table 3. The results show that when the blood sugar fell markedly the carbon dioxide tension of the arterial blood was significantly reduced. On intravenous injections of dextrose the carbon dioxide tension of the arterial blood rose together with the concentration of sugar. It is found, frequently, however, that the increase in carbon dioxide tension may

not reach the control level although the blood sugar has been restored to the previous level. The results of the experiments confirm the observations on psychotic patients already described. They are also similar to observations in experiments carried out on morphinized dogs which were briefly reported on earlier.[1b]

In summary, it may be said that insulin hypoglycemia in man and in animals produces a fall in the sugar and carbon dioxide tension of arterial blood. Both phenomena are reversible on administration of dextrose (intravenously) or sucrose (by stomach tube).

Effects of Stimulation of the Central Sympathetic Nervous System on the Dextrose Concentration, Carbon Dioxide Tension and p_H of Arterial Blood.—In order to evaluate the experiments described, further

TABLE 4.—*Effects of Excitation on the Sugar, Carbon Dioxide Tension and p_H of Arterial Blood in Dogs*

Dog no. 41; weight 12.6 Kg.	
10:10 a. m.:	Blood sugar, 105.3 mg. per 100 cc.; carbon dioxide, 33.2 mm.; p_H, 7.46
10:55 a. m.:	Dog tied to table, annoyed by cat. Struggling until 11:25 a. m.
11:25 a. m.:	Blood sugar, 117.2 mg. per 100 cc.; carbon dioxide, 26.4 mm.; p_H, 7.47
1:20 p. m.:	Dog quiet. Blood sugar, 96.7 mg. per 100 cc.; carbon dioxide, 29.9 mm.; p_H, 7.52
2:05 p. m.:	Dog tied to table. Struggling
2:40 p. m.:	Blood sugar, 98.9 mg. per 100 cc.; carbon dioxide, 26.1 mm.; p_H, 7.51
Dog no. 42; weight 8.6 Kg.	
10:00 a. m.:	Blood sugar, 73.1 mg. per 100 cc.; carbon dioxide, 39.5 mm.; p_H, 7.31
10:55 a. m.:	Dog tied to table; stimulated intermittently with Harvard inductorium, coil at distance of 3 cm. Marked excitement and struggle
11:11 a. m.:	Blood sugar, 178.4 mg. per 100 cc.; carbon dioxide, 17.8 mm.; p_H, 7.32
Dog no. 43; weighed 11.7 Kg. Fed 3 Gm. of thyroid daily ten days prior to experiment	
10:30 a. m.:	Blood sugar, 70.4 mg. per 100 cc.; carbon dioxide, 42 mm.; p_H, 7.38
11:20 a. m.:	Dog tied to table, stimulated with faradic current, as in the preceding experiment. Marked struggle
11:40 a. m.:	Blood sugar, 92.9 mg. per 100 cc.; carbon dioxide, 27.5 mm.; p_H, 7.42

studies were made on the effects of stimulation of the central sympathetic nervous system on the dextrose concentration, the p_H and the carbon dioxide tension of the arterial blood.

In the first group of experiments, quiet dogs, after blood had been analyzed for control purposes, were brought into a state of excitation either by being confronted with a cat or by being tied down to the table and subjected to painful stimuli.

Under these circumstances a rise in blood sugar was seen, as has been observed by Cannon [3] and his collaborators, as well as a fall of carbon dioxide tension of the arterial blood. Both processes were reversible when the dog had quieted sufficiently. As experiment 41 in table 4 indicates, such experiments may be carried out repeatedly on the same dog with similar effects. It was found that the carbon dioxide tension of the blood is more easily altered than the sugar concentration. Not infrequently, struggling caused a fall of the carbon dioxide tension although the blood sugar was practically unaltered. If the animal is

excitable, the effects may be marked for both the blood sugar and the carbon dioxide tension. Experiment 42 (table 4) shows a great fall of carbon dioxide tension accompanied by a marked rise of sugar. It is interesting to note that in spite of the fact that the carbon dioxide tension fell from 39.5 to 17.8 mm., the p_H of the blood remained constant.

It was thought that the effects of metrazol on the sympathetic nervous system may be similar to those of general excitation, such as was produced in the dog under conditions which led to a marked struggle. In an earlier investigation, Gellhorn and Darrow [8] showed that metrazol is a stimulant of the sympathetic nervous system, leading to continued discharges from the sympathetic centers, as shown by records from the nictitating membrane (automatic contractions), pupillary dilation and

TABLE 5.—*Effect of Metrazol on Sugar, Carbon Dioxide Tension and p_H of Arterial Blood of Dogs*

Dog no. 36; weight 10.5 Kg.	
10:20 a. m.:	Blood sugar, 81.7 mg. per 100 cc.; carbon dioxide, 33.6 mm.; p_H, 7.43
11:02 a. m.:	Metrazol, 45 mg. per Kg. subcutaneously
11:11 a. m.:	Vomiting, defecation, retching, fidgeting
11:32 a. m.:	Blood sugar, 110.9 mg. per 100 cc.; carbon dioxide, 30.1 mm.; p_H, 7.36
1:03 p. m.:	Blood sugar, 76.3 mg. per 100 cc.; carbon dioxide, 35.0 mm.; p_H, 7.33
Dog no. 37; weight 8.6 Kg.	
10:20 a. m.:	Blood sugar, 76.3 mg. per 100 cc.; carbon dioxide, 41.8 mm.; p_H, 7.37
11:05 a. m.:	Metrazol, 45 mg. per Kg. subcutaneously
11:38 a. m.:	Blood sugar, 81.7 mg. per 100 cc.; carbon dioxide, 31.2 mm.; p_H, 7.42
12:02 p. m.:	Blood sugar, 138.7 mg. per 100 cc.; carbon dioxide, 33.3 mm.; p_H, 7.40
1:03 p. m.:	Blood sugar, 140.9 mg. per 100 cc.; carbon dioxide, 34.6 mm.; p_H, 7.37
Dog no. 38; weight 6.4 Kg.	
11:23 a. m.:	Metrazol, 45 mg. per Kg. subcutaneously
12:05 p. m.:	Blood sugar, 110.9 mg. per 100 cc.; carbon dioxide, 37.5 mm.; p_H, 7.40
	Retching, vomiting, twitching
12:28 p. m.:	Typical metrazol convulsions; opisthotonos
12:41 p. m.:	Blood sugar, 184.9 mg. per 100 cc.; carbon dioxide, 24.9 mm.; p_H, 7.20
2:08 p. m.:	Blood sugar, 167.7 mg. per 100 cc.; carbon dioxide, 35.6 mm.; p_H, 7.44
3:45 p. m.:	Blood sugar, 115.2 mg. per 100 cc.; carbon dioxide, 37.4 mm.; p_H, 7.40

rise in blood pressure. It therefore seemed of interest to investigate whether the inverse relationship between the sugar and the carbon dioxide tension of the blood which was observed during excitation would hold true for conditions brought about by the administration of metrazol.

The experiments of table 5 show that metrazol raised the sugar content and lowered the carbon dioxide tension of the blood. This effect occurred not only in the presence but also in the absence of metrazol convulsions. Experiment 36 shows that half an hour after the injection of metrazol the blood sugar reached the highest and the carbon dioxide tension the lowest level. One and one-half hours later the blood sugar had fallen and the carbon dioxide tension had risen to the control level. Experiment 37 represents a reaction of slightly different type,

8. Gellhorn, E., and Darrow, C. W.: The Action of Metrazol on the Autonomic Nervous System, Arch. internat. de pharmacodyn. et de thérap. **62**: 114, 1939.

as here the blood sugar continued to rise for several hours after the injection of metrazol whereas the carbon dioxide tension reached a minimum one-half hour after the injection and then rose gradually. The results seemed to indicate that in this case the effect of metrazol continued for several hours, since even two hours after the injection of the drug the carbon dioxide tension was decidedly below and the sugar above the control level in the blood.

Experiment 38 in table 5 shows the effect of metrazol on the sugar, the carbon dioxide tension and the p_H of the blood of a dog in which it produced marked convulsions. Similar to the record of experiment 36, an inverse relationship between the sugar and the carbon dioxide tension of the blood was found. A maximum sugar content and a minimum carbon dioxide tension occurred shortly after the metrazol convulsions.

TABLE 6.—*Effect of Epinephrine Hydrochloride on the Sugar, Carbon Dioxide Tension and p_H of Arterial Blood in Dogs*

Dog no. 21; weight 16.8 Kg.	
10:35 a. m.:	Blood sugar, 73.1 mg. per 100 cc.; carbon dioxide, 48.0 mm.; p_H, 7.27
11:40 a. m.:	Epinephrine hydrochloride (1:1,000), 0.05 cc. per Kg. subcutaneously
12:23 p. m.:	Blood sugar, 101.1 mg. per 100 cc.; carbon dioxide, 43.8 mm.; p_H, 7.26
1:25 p. m.:	Blood sugar, 120.9 mg. per 100 cc.; carbon dioxide, 39.0 mm.; p_H, 7.27
3:15 p. m.:	Blood sugar, 104.1 mg. per 100 cc.; carbon dioxide, 42.1 mm.; p_H, 7.29
Dog no. 22; weight 14.8 Kg.	
10:20 a. m.:	Blood sugar, 76.5 mg. per 100 cc.; carbon dioxide, 41.6 mm.; p_H, 7.32
11:05 a. m.:	Epinephrine hydrochloride (1:1,000), 0.05 cc. per Kg. subcutaneously
11:30 a. m.:	Blood sugar, 78.7 mg. per 100 cc.; carbon dioxide, 36.4 mm.; p_H, 7.35
12:52 p. m.:	Blood sugar, 99.8 mg.per 100 cc.; carbon dioxide, 28.0 mm.; p_H, 7.29
2:10 p. m.:	Blood sugar, 87.3 mg. per 100 cc.; carbon dioxide, 36.7 mm.; p_H, 7.34 Quiet, resting
3:25 p. m.:	Blood sugar, 76.5 mg. per 100 cc.; carbon dioxide, 40.5 mm.; p_H, 7.33

Later the sugar and carbon dioxide tension of the blood approached the normal level. It is interesting to note that this is the only experiment in which a significant change in p_H was found. The convulsions led obviously to a marked increase in lactic acid concentration in the blood. It is worthy of mention that in the absence of severe convulsions even greater changes in the carbon dioxide tension of the blood (compare experiment 42, table 4) may be fully compensated for by corresponding changes in the alkali reserve, so that no change in p_H results.

A final series of experiments is presented in table 6, in which the effect of epinephrine is reproduced. It was found that the subcutaneous injection of 0.05 cc. of a 1:1,000 solution of epinephrine hydrochloride per kilogram of body weight produced marked signs of hyperirritability. In line with this result is the fact that epinephrine produced a rise in the sugar and a fall in the carbon dioxide tension of the blood. In these cases no significant change in the p_H of the blood was observed. The effects were reversible.

COMMENT

The experiments show that when general excitation is produced either reflexly, by painful stimuli calling forth a violent struggle, or directly, by the injection of metrazol or epinephrine (concerning the inhibitory action of small doses of epinephrine on the central nervous system, see Darrow and Gellhorn [9] and Gellhorn, Darrow and Yesinick [10]), the blood sugar rises and the carbon dioxide tension of the arterial blood falls. Since it is well known that hypothalamic stimulation is associated with markedly increased respiration (Ranson and Magoun [11] and Bard [12]) and elevation of blood sugar, it may be assumed that the lowering of carbon dioxide tension of the arterial blood and the hypoglycemia observed in our experiments were due to excitation of sympathetic centers in the hypothalamus.

It is interesting to note that in spite of marked changes in the carbon dioxide tension of the blood in insulin hypoglycemia, the p_H remains unchanged provided that no convulsions occur. In view of the fact that the p_H of the brain seems to increase in hypoglycemia (Marshall and his co-workers [13]), it is unlikely that the diminished carbon dioxide tension of the arterial blood in insulin hypoglycemia is caused by an increase in fixed acids. It is more probable that hypothalamic stimulation, induced directly or indirectly, is associated with a lower carbon dioxide tension and that this in turn, leads to lowering of the alkali reserve, thereby maintaining the p_H constant. The mechanism seems to be similar to that assumed by Henderson [14] to hold for anoxia.

The paradox that the carbon dioxide tension is lowered during insulin hypoglycemia, showing that in this condition the sugar and the carbon dioxide of the blood are directly related, whereas in experiments involving painful stimuli and the injection of metrazol or epinephrine an indirect relationship is found to exist is best explained by the assumption that insulin hypoglycemia leads to stimulation of the sympathetico-

9. Darrow, C. W., and Gellhorn, E.: The Effects of Adrenalin on the Reflex Excitability of the Autonomic Nervous System, Am. J. Physiol. **127**:243, 1939.

10. Gellhorn, E.; Darrow, C. W., and Yesinick, L.: Effect of Epinephrine on Convulsions, Arch. Neurol. & Psychiat. **42**:826 (Nov.) 1939.

11. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

12. Bard, P.: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**: 490, 1928.

13. Marshall, C.; McCulloch, W. S., and Nims, L. F.: p_H of the Cerebral Cortex and Arterial Blood Under Insulin, Am. J. Physiol. **125**:680, 1939.

14. Henderson, Y.: Adventures in Respiration, Baltimore, Williams & Wilkins Company, 1938.

adrenal apparatus. In favor of this assumption is the fact that alterations in carbon dioxide tension occur only below a certain critical level of blood sugar. This is in agreement with earlier work of Gellhorn and his collaborators in which it was found that increased sensitivity of the sympatheticoadrenal system occurred at low levels of the blood sugar. Similar observations were made by Cannon, McIver and Bliss [15] and Schlossberg, Sawyer and Bixby.[16] Particularly interesting is the finding of Ernstene, Riseman, Stern and Alexander [17] that during hypoglycemia an increase in the heart rate and the minute volume of the heart occurred in cats with denervated hearts and normal adrenal glands. If, however, the adrenal glands were denervated, no increase in the heart rate was observed and the minute volume was decreased. Obviously, the condition produced in experiments with insulin hypoglycemia and that in experiments with central or reflex stimulation of the hypothalamus have excitation of the sympatheticoadrenal system in common. However, the effect of this excitation on the blood sugar is masked in the insulin experiments, but its presence is evidenced by the much greater fall in blood sugar produced with a given amount of insulin in adrenalectomized animals.[17a] Studies of the heart rate and the electrocardiogram seem to demonstrate in general the same features (Hadorn [18]). That Himwich and his associates [19] found signs of predominance of the vagus nerve in cases of insulin hypoglycemia is probably due to the fact that they investigated the effects of this condition at extremely low levels of the blood sugar. It is not improbable that under these conditions the sympatheticoadrenal system, which is first called into action, ceases to react and that thereby an imbalance is brought about in favor of the parasympathetic system. This was shown by the investigations of Himwich and his collaborators. In only 1 of the representative cases which they described was there vagal stimulation, and this was a case in which

15. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XIII. A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

16. Schlossberg, T.; Sawyer, M. E. M., and Bixby, E. M.: Studies of Homeostatis in Normal, Sympathectomized and Ergotaminized Animals: III. The Effect of Insulin, Am. J. Physiol. **104**:190, 1933.

17. Ernstene, A. C.; Riseman, J. E. F.; Stern, B., and Alexander, B.: The Mechanism of the Circulatory Changes Accompanying Insulin Hypoglycemia, Am. J. Physiol. **111**:440, 1935.

17a. Britton, S. W.; Geiling, E. M. K., and Calvery, H. O.: Medulliadrenal Secretion and Carbohydrate Metabolism, Am. J. Physiol. **84**:141, 1928.

18. Hadorn, W.: Untersuchungen des Herzens im hypoglykämischen Schock, Arch. f. Kreislaufforsch. **2**:70, 1937.

19. Himwich, H. E.; Frostig, J. P.; Fazekas, J. F., and Hadidian, Z.: The Mechanism of the Symptoms of Insulin Hypoglycemia, Am. J. Psychiat. **96**: 371, 1939.

extremely low blood sugar persisted for several hours. In the other cases signs of vagal stimulation were entirely absent, but sympathetic excitation prevailed. In extreme hypoglycemia the condition of the autonomic nervous system may be similar to that in the final stage of asphyxia. Whereas asphyxia at first produces marked sympathetico-adrenal excitation, it leads finally to a condition in which at low blood pressure slow pulses characteristic of vagal stimulation occur. Within physiologic limits, however, both asphyxia and insulin hypoglycemia seem to elicit predominantly signs of sympathetic, and not of parasympathetic, excitation. It is this phase of insulin hypoglycemia which seems therapeutically important (Gellhorn [1b]).

Since it is well known that the carbon dioxide tension is lowered in anoxia, the present investigations present new evidence for a similarity of the effects of anoxia and those of hypoglycemia on the central nervous system.

SUMMARY

When insulin leads to a fall of the blood sugar below 50 mg. per hundred cubic centimeters, this is accompanied by a fall in the carbon dioxide tension of the alveolar air. Restoration of the blood sugar level leads to a rise in the carbon dioxide tension (experiments on schizophrenic patients).

In deep coma the carbon dioxide tension of the alveolar air at a given level of the blood sugar is higher than at similar levels before coma occurs.

The carbon dioxide tension of the arterial blood is lowered during insulin hypoglycemia and restored to control levels in unanesthetized dogs on injection of dextrose.

General excitement induced by painful stimuli and struggle leads to rise of the blood sugar and lowering of the carbon dioxide tension of the arterial blood in unanesthetized dogs.

Injection of metrazol or epinephrine has effects on the carbon dioxide tension and the sugar of arterial blood similar to those of general excitement. All effects are reversible and are not accompanied by a change in the p_H of the arterial blood.

It is assumed that excitation of the sympathetic nerve centers is responsible for the decrease in carbon dioxide tension of the arterial blood and of the alveolar air.

PARAPLEGIA IN FLEXION

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Involuntary flexion of the lower limbs is seen in a variety of conditions. It may be due, for instance, to changes in the muscles themselves, as in the myopathic type of senile paraplegia,[1] or to the unopposed action of the flexor muscles of the hip following injury to the cauda equina. Spasm of the flexor muscles is associated at times with painful disorders of the lumbar portion of the spine even when objective evidence of involvement of the nervous system is lacking. Spastic paraplegia in flexion resulting from a release of reflex mechanisms in the lumbosacral part of the cord, on the other hand, is of more than passing interest. To any one interested in the physiologic implications of lesions of the spinal cord and the general problem of spastic paralysis few subjects can be more fascinating.

Contracture in flexion and involuntary movements of the lower extremities were described in cases of tumor involving the thoracic portion of the spinal cord reported by Colin[2] in 1824 and by Hardy[3] in 1834. In 1837 Ollivier[4] gave details of 3 cases in which flexion contracture had developed; the condition was associated with Pott's disease in the first case, multiple softening of the cord in the second and syringomyelia in the third. In a case reported by Schultze[5] in 1883, the contracture developed after apparent complete transverse

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This study was begun in the Section on Neurology of the Mayo Clinic, at the suggestion of Dr. John B. Doyle, now of Los Angeles. Dr. Henry W. Woltman helped in the reexamination of clinical records and gave permission to use case material collected in the Mayo Clinic.

1. Lhermitte, J. J.: Étude sur les paraplégies des vieillards, Thesis, Paris, no. 160, Paris, L. Marétheux, 1907.

2. Colin, M., 1824, cited by Ollivier.[4]

3. Hardy, M.: Observation de tumeur encéphaloïde developpée dans l'arachnoïde rachidienne et determinant la compression de la moelle épinière, Arch. gén. de méd. **5**:229, 1834.

4. Ollivier, C. P.: De la moelle épinière et de ses maladies, ed. 3, Paris, Méguignon-Marvis Père et Fils, 1837.

5. Schultze, F.: Beitrag zur Lehre von der secundären Degeneration im Rückenmark des Menschen nebst Bemerkungen über die Anatomie des Tabes, Arch. f. Psychiat. **14**:359, 1883.

destruction of the cord by trauma; in a case reported the same year by Démange [6] it was due to cerebral vascular disease.

Both Charcot and Sternberg [7] commented on the exaggeration of the flexor reflex which accompanied transition from spastic paraplegia in extension to one in flexion. Babinski,[8] impressed by the absence of degeneration of the pyramidal tracts in 3 cases reported in 1899, expressed the view that irritation of these tracts by the lesion might have caused the limbs to assume the flexed position. Foerster,[9] in 1906, declared that it was the involuntary movements of flexion, induced by external stimuli and becoming progressively more marked with accentuation of the paralysis, which, in his opinion, brought about the flexion contracture so frequently observed in cases of progressive spastic paraplegia. Babinski [10] later identified the involuntary movements with reflexes of defense and attributed the contracture to exaggeration of these reflexes.

Walshe [11] correlated the reflex phenomena of spastic paralysis with Sherrington's observations. He pointed out that paraplegia in extension due to involvement of the pyramidal tracts was characterized by exaggeration of tonic reflexes in the extensor muscles. In cases of more extensive lesions of the cord extrapyramidal pathways were likely to be involved with consequent loss of extensor tone and exaggeration of the flexor reflexes, as in the spinal animal. Böhme [12] emphasized the importance of decubitus ulcers as a source of continuous stimulation of a nocuous character in the development of a flexion contracture. The frequently associated decline in the patient's general condition, he asserted, was also a contributing factor by reason of its depressing effect on the extensor reflexes. Riddoch,[13] in his studies of complete tran-

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6. Démange, E.: Contributions à l'étude: I. Des tremblements prae- et post-hémiplégiques; II. Des hémiplégies bilatérales, Rev. de méd., Paris **3**:371, 1883.

7. Charcot, J. M.: Lectures on the Diseases of the Nervous System, London, New Sydenham Society, 1881. Sternberg, M.: Die Sehnenreflexe und ihre Bedeutung für die Pathologie des Nervensystems, Vienna, Franz Deuticke, 1893.

8. Babinski, J.: Sur une forme de paraplégie spasmodique consécutive à une lésion organique et sans dégénération du système pyramidale, Bull. et mém. Soc. méd. d. hôp. de Paris **16**:342, 1899.

9. Foerster, O.: Die Kontrakturen bei Erkrankungen der Pyramidenbahn, Berlin, S. Karger, 1906.

10. Babinski, J.: Contracture tendino-réflexe et contracture cutanéo-réflexe, Rev. neurol. **20**:77, 1912.

11. Walshe, F. M. R.: The Physiological Significance of the Reflex Phenomena in Spastic Paralysis of the Lower Limbs, Brain **37**:267, 1914.

12. Böhme, A.: Ueber die reflektorischen Leistungen des menschlichen und tierischen Rückenmarks, Deutsches Arch. f. klin. Med. **121**:129, 1916.

13. Riddoch, G.: The Reflex Functions of the Completely Divided Spinal Cord in Man Compared with Those Associated with Less Severe Lesions, Brain **40**:264, 1917.

section of the cord in man, likewise observed this peculiar susceptibility of the extensor reflexes to changes in the general condition. In a later paper [14] he stated that unusual activity of the flexor reflexes was apt to be due to irritation from bed sores, especially those near the feet, where the threshold was lowest.

Foerster [15] has made three observations which seem to prove that the flexor muscles in the type of contracture under consideration are actually in a spastic state: First, using an action current, he has demonstrated exaggeration of the stretch reflex in these muscles; second, he has found that the hamstring muscles when exposed at operations for the relief of flexion contracture respond with vigorous clonus to traction on their cut tendons; third, he has relieved the contracture by section of the posterior lumbosacral roots.

CLINICAL CHARACTERISTICS

In well developed paraplegia in flexion the patient is found lying on his back or side with the thighs flexed on the pelvis and more or less adducted, the knees acutely flexed and the feet somewhat dorsiflexed. The abdominal muscles, notably the recti, are often tightly contracted. In cases of extreme severity the thighs are in contact with the abdomen and the heels touch the buttocks. Because of the frequently recurring movements of flexion, however, the contracture is apt to be variable in degree. It may be intermittent, especially in the beginning, but any sort of stimulus is likely to cause the extended limbs to resume the flexed position. Passive extension is generally possible to only a slight extent, and the effort may evoke a lively jerking of the hamstring muscles. The muscles may appear wasted.

It is generally agreed that the involuntary movements are reflex in nature and identical with the withdrawal reaction. They appear to be induced by any number of fortuitous stimuli, such as pressure of the bedcovers on the patient's toes, distention of the bladder or rubbing of the parts against the bed in consequence of voluntary movements of the upper portion of the body. Øwre [16] pointed out that irritation of the skin resulting from the movements would contribute to ulceration, thus setting up a vicious circle. The withdrawal reaction, variously referred to as the reflex of defense, flexion reflex synergy or, more simply, the flexor reflex, consists of a contraction of the rectus abdominis muscle, the flexors of the hip, the flexors of the knee and the dorsiflexors of the

14. Riddoch, G.: The Practical Significance of the Mass-Reflex in the Treatment of Injuries to the Spinal Cord, Lancet **2**:839, 1918.

15. Foerster, O.: Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, pp. 1-403.

16. Øwre, A.: Reflexes of Spinal Automatism, Acta psychiat. et neurol. **1**: 260, 1936.

foot and toes. Difference of opinion seems to exist as to whether the thigh is abducted or adducted in the flexor reflex.[17] In cases in which there was no flexion contracture I have been able to confirm Foerster's statement [15] that the thigh is abducted during the response of triple flexion and adducted during that of triple extension. Although the flexor response may be elicited at times by a mere touch, nocuous stimuli—stimuli which normally would be distinctly unpleasant, if not painful—are the most effective. The threshold is lowest in the sole, but the reflexogenous zone may extend well up on the trunk, depending on the level of the lesion.

There is little evidence of the extension reflex synergy once a flexion contracture has developed. Contraction of the flexor muscles in the withdrawal reaction is succeeded not, as a rule, by active contraction of the extensors, but merely by limited relaxation of the flexors. The nearest approach I have ever seen to a homolateral extensor reflex from nocuous stimulation of the upper part of the thigh was sufficient relaxation of the flexor muscles to permit passive extension of the limb in 1 case. This was a striking example of reciprocal innervation; although there was little, if any, active contraction of the extensor muscles, there was considerable inhibition of their antagonists. Foerster [15] has succeeded in overcoming flexor spasms in a like manner. Flexion of the one limb is generally accompanied, if the stimulus is sufficiently strong, by flexion of the other, although some indication of a crossed extensor response is occasionally noted.

Babinski [18] was impressed by the not infrequent absence or relative sluggishness of the knee and ankle jerks in these cases, whereas Walshe [11] stressed the equally significant fact that the hamstring reflexes remained active. Although the patellar reflex may be weak, or even abolished, the achilles reflex does not appear to be depressed as frequently or to so great an extent. Øwre [16] found that the patellar reflex in its phase of relaxation was often sharp and aplastic, his experience being similar to that of Riddoch,[19] who commented on the quick falling away of both the knee and the ankle jerk in cases of complete transection of the cord. In general, it may be said that, in keeping with the law of reciprocal innervation, the more extreme the degree of flexion at the knee the greater will be the loss of tone in the vastus cruris muscles. A commensurate loss of tone in the triceps surae muscle would hardly be expected, since dorsiflexion of the foot is seldom marked. When, as not infrequently happens, the feet are in plantar flexion, ankle clonus

17. Riddoch.[13] Øwre.[16]

18. Babinski, J.: Paraplégie spasmodique avec contracture en flexion et contractions musculaires involuntaires, Rev. neurol. **19**:132, 1911.

19. Riddoch, G.: The Clinical Picture of Complete Transverse Division of Spinal Cord, M. Sc. **5**:49, 1921.

may be obtainable. Babinski's sign and its several modifications, being integral parts of the flexor reflex,[11] are nearly always present, and one can usually elicit the reflexes of Rossolimo and Mendel and Bechterew.

Although the muscles are often more spastic than weak in the ordinary variety of paraplegia, paralysis is usually complete in the flexion type. Babinski [18] attached significance to the slight amount of anesthesia in his cases, but in cases of involvement of the spinal cord sensation is in general considerably diminished, when not abolished. André-Thomas [20] commented on the fact that the involuntary movements of the limbs may be painful even when the patient is not conscious of these movements as such and loss of sensation to pain is profound. Control of the sphincters is usually lost, automatic emptying of the bladder and bowel being the rule.

PATHOLOGIC STATES CAUSING PARAPLEGIA IN FLEXION

Because of its comparative frequency in cases of compression of the cord, it was formerly believed that the presence of a contracture in flexion would permit certain diagnostic conclusions.[21] It has since become apparent, however, that any pathologic state capable of releasing reflex mechanisms in the lower spinal segments may give rise to a contracture in flexion, the main requirement being that the reflex pathways of the lumbosacral region of the cord remain functionally intact.

TUMOR OF THE SPINAL CORD

In 7 cases of extramedullary tumor of the cervical or thoracic part of the cord with contracture in flexion reported in the literature, the transverse lesion was considerably less than complete from an anatomic standpoint. Flexion contracture came on in Hardy's case [3] eighteen months after the limbs were totally paralyzed, but the interval was much shorter in the others. According to the history in Babinski's [8] case, the patient, a woman aged 77, fell with her lower extremities completely paralyzed six months after onset of weakness and at once a flexion contracture developed. Complete paraplegia preceded flexion contracture by periods of three and four months, respectively, in the cases of Coyon and Barré [22a] and of Schultze.[22b] The contracture was developing as

20. André-Thomas: La paraplégie spasmodique avec contracture variable, Clinique **8**:388 and 405, 1913; abstracted, Rev. neurol. **30**:204, 1916.

21. Babinski, J., and Jarkowski, J.: Sur le diagnostic des compressions spinales, Rev. neurol. **39**:670, 1923.

22. (*a*) Coyon, A., and Barré, A.: Paraplégie "type Babinski" chez un sujet atteint de la maladie de Recklinghausen, Nouv. iconog. de la Salpêtrière **27**:81, 1914. (*b*) Schultze, F.: Zur Diagnostik und operativen Behandlung der Rückenmarkshautgeschwülste, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **12**:153, 1903. (*c*)

(Footnote continued on next page)

early as three months after onset of symptoms in Verger and Massia's case,[22c] and evidently came on in less than a year in the cases of Schaller and Gilman [22d] and of Edes.[22e] The tumor had barely indented the cord in Coyon and Barré's case, but this case is exceptional in view of the abrupt onset of paraplegia and the patient's death from sepsis four months later.

Tendency to flexion was said to have been present from the onset of weakness in Claude's case [23] of multiple tumors involving the cord. In the following case the lower extremities began to flex about the time all voluntary motion was lost, ten months after onset, and were in a permanently flexed position four months later.

CASE 1.—*History.*—A woman aged 53 was registered at the Mayo Clinic on Jan. 2, 1930. She had begun to complain of pain in the right hip and thigh and of occasional giving way of the right leg in September 1928. Incontinence of urine followed hysterectomy in January 1929, and from this time she was prevented from walking by frequent giving way of both lower extremities. Voluntary motion had been lost in the right lower limb for eight months and in the left for six months. The limbs began to flex involuntarily six months prior to admission, and there had been a pronounced flexion contracture for at least two months.

Examination.—The patient lay in bed with her thighs and legs flexed to the extent that the heels were almost in contact with the buttocks; the feet and toes were slightly dorsiflexed. The abdominal muscles were tightly contracted. No voluntary movement was possible, and the legs could be passively extended to only a very limited degree. Small ulcers were noted on one heel and the buttocks and scars of recent burns were present about the knees, but the patient appeared to be in fair general condition. Involuntary flexion movements of the lower extremities were frequent and evidently painful. There was complete anesthesia for all qualities up to the level of the sixth dorsal dermatome. Contraction of the flexor muscles of the lower limbs and of the abdominal muscles could be induced by pricking the legs, thighs and lower portion of the abdomen with a pin. The patellar reflexes could not be elicited, but the achilles reflexes were slightly hyperactive and the hamstring reflexes were definitely hyperactive. The reflexes of Babinski, Chaddock and Oppenheim were present on both sides. The spinal fluid contained 120 mg. of total protein in a hundred cubic centimeters and 7 lymphocytes in a cubic millimeter. Queckenstedt's test revealed partial blocking of the subarachnoid space.

Operation and Course.—Operation was performed on Jan. 7, 1930 by Dr. A. W. Adson, who removed an endothelioma lying to the front and the right side of the cord opposite the bodies of the sixth and seventh dorsal vertebrae. The cord had been compressed at this level to about two-thirds its normal volume. A feeble patellar reflex was obtained on one occasion during the patient's conva-

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Verger, H., and Massias, C.: Paraplégie en flexion, Presse méd. **31**:980, 1923. (*d*) Schaller, W. F., and Gilman, P. K.: Spastic Paraplegia in Flexion, Arch. Neurol. & Psychiat. **10**:512 (Nov.) 1923. (*e*) Edes, R. T.: Paraplegia with Contraction, Eschars, Congestion and Sclerosis of the Spinal Cord from Compression by a Tumor, Boston M. & S. J. **91**:306, 1874.

23. Claude, H.: Compression médullaire et hystérie, Encéphale **2**:359, 1910.

lescence, but the flexion contracture persisted. In a letter received a year later it was stated that she was no better and was still greatly distressed by the frequent involuntary movements of the lower limbs.

In referring to the situation of the growth, Elsberg [24] said:

> The tumors have been on the ventral or ventrolateral aspect of the cord if they are intradural. Quite frequently we have seen the flexion type with extradural tumors which are, of course, on the anterior aspect, or mostly on the anterior aspect.

Of the group of 7 cases of solitary extramedullary tumor referred to previously, the growth was extradural in 2 and had a posterior location with reference to the cord in a like number. The growth was lateral to the cord in 2 cases and was anterolateral or anterior in the remaining 3 cases.

In 4 cases collected from the literature,[25] flexion contracture was associated with apparent complete transverse destruction of the dorsal or cervical region of the cord by an extramedullary tumor. The interval between onset of total paraplegia and developing of flexion contracture ranged from eighteen months, in the case of Gerhardt [25a] to more than eight years, in that of Senator.[25b] The limbs assumed the flexed position subsequent to the appearance of decubitus ulcers in both these cases. Raymond and Cestan [25c] reported a second case of practically complete transection of the cord by slow compression in which spastic paraplegia in extension persisted until death. This case and others of a similar nature will be discussed later. Paraplegia in flexion existed in 3 of 51 cases of intramedullary tumor studied by Kernohan, Woltman and Adson.[26]

In the course of gradual compression of the cord a condition may be encountered which Foix [27] termed paraplégie hyperspasmodique. Although the extensor muscles are very spastic at this stage and clonic spasms are frequent, flexor reflexes can be elicited. As compression continues there is apt to be an increase in the amplitude of the involuntary movements of flexion, accompanied by reduction of extensor tone. Although the struggle between the two opposing groups of muscles may be fairly even for a time, the limbs finally come to remain in a flexed position for progressively longer intervals until the stage of

24. Elsberg, C., in discussion on Schaller and Gilman,[22d] p. 514.

25. (*a*) Gerhardt, D.: Ueber das Verhalten der Reflexe bei Querdurchtrennung des Rückenmarks, Deutsche Ztschr. f. Nervenh. **6**:127, 1895. (*b*) Senator, H.: Zwei Fälle von Querschnittserkrankung des Halsmarks, Ztschr. f. klin. Med. **35**:1, 1898. (*c*) Raymond and Cestan, R.: Quelques remarques sur la paraplégie spasmodique par tumeur médullaire, Rev. neurol. **10**:174, 1902. (*d*) Colin.[2]

26. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord, Arch. Neurol. & Psychiat. **25**:679 (April) 1931.

27. Foix, C.: Rapport sur les compressions médullaires, Rev. neurol. **39**:610, 1923.

permanent flexion contracture is reached. The patient whose history follows was in the stage of "hyperspasmodic" paraplegia when the tumor was removed. Apparently as a result of further damage to the cord at the time of the surgical procedure, the extensor reflexes were depressed, and, after the appearance of a deep trophic ulcer, the flexor reflexes were progressively enhanced. A flexion contracture resulted, but after healing of the ulcer and improvement in the general condition the limbs returned to a position of extension. Kraus and Rabiner [28] saw flexion contracture develop after removal of an extradural tumor lying posterior to the dorsal portion of the cord.

CASE 2.—*History.*— A man aged 36, who was registered at the Mayo Clinic on Sept. 16, 1929, had complained of pain in the back and legs as early as 1924 and of gradual loss of use of the lower extremities, beginning in 1927, when weakness of the right leg was first noticed.

Examination.—The lower limbs were completely paralyzed and very spastic. The knee and ankle jerks were exceedingly hyperactive, and the hamstring reflexes were slightly hyperactive. The reflexes of Babinski, Chaddock, Rossolimo, Mendel and Bechterew, Oppenheim and Schaefer were present bilaterally. Abrupt withdrawal movements of either leg in response to various stimuli were quickly checked by an extensor rebound and were often followed by violent clonus of the extensor muscles. The abdominal reflexes were absent. Vibratory sensibility was almost entirely lost over the malleoli and was markedly diminished elsewhere in the lower extremities; sense of position was lost in the toes of the right foot and impaired in the toes of the left. Superficial sensation was diminished to a generally slight and variable degree from the hips down. The spinal fluid had a yellowish tinge and contained 1,000 mg. of total protein in a hundred cubic centimeters. Queckenstedt's test revealed total blocking of the subarachnoid space. Two days after spinal puncture loss of superficial sensation was more definite. particularly that for pain and temperature, which was lost in the left lower extremity and diminished as high as the fifth dorsal segmental area on the left side of the trunk.

Operation and Course.—On Sept. 26, 1929 Dr. W. M. Craig removed a neurofibroma from the right anterolateral aspect of the cord opposite the body of the second dorsal vertebra. The cord was compressed at this level to one-fourth its normal size. After operation anesthesia was more marked and control of the bladder was lost; the knee and ankle jerks became sluggish and for a time were unobtainable on the right side, but were later moderately hyperactive. A deep ulcer developed over the right greater trochanter; the bladder became infected, and involuntary flexion movements of the lower extremities grew troublesome. When I examined the patient on Dec. 26, 1929, his limbs were flexing every minute or two, superficial sensation was abolished from the nipples down and sense of position was lost in the feet. The patellar reflexes were slightly hyperactive; the right achilles reflex was moderately hyperactive, and the left achilles reflex was very hyperactive. The legs were definitely fixed in a flexed position on Feb. 28, 1930, according to a note made on that date.

When the patient returned in May 1931, the lower limbs were still in a flexed position and the abdominal muscles were tightly contracted. The bladder had been

28. Kraus, W. M., and Rabiner, A. M.: On the Production of Neuromuscular Patterns by Release of Spinal Integrations After Decerebration, J. Neurol. & Psychopath. **3**:209, 1922.

functioning automatically for the past seven months, and sacral ulcers had been present for the past five months. The deep ulcer in the right thigh was healing. The patellar reflexes were moderately hyperactive, and the achilles reflexes were normally active, while the hamstring reflexes were decidedly hyperactive. The lower limbs, especially the left, could be passively extended with the aid of nocuous stimulation of the upper portion of the thigh (homolateral extensor reflex), and there was indication of a crossed extensor reflex. Reflexes of defense were active.

The family physician, in a letter dated July 29, 1932, stated that the ulcers had healed and that the spasms were diminishing in intensity. In a note made May 1, 1933, when the patient returned for further examination, it was recorded that the limbs had been in an extended position for the past six months. The extensor muscles were again very spastic, the patellar and achilles reflexes being, if anything, more hyperactive than before operation, and the upper limit of anesthesia had receded to the level of the ensiform cartilage. Queckenstedt's test revealed no evidence of block, and the spinal fluid contained only 40 mg. of total protein in a hundred cubic centimeters.

OTHER VARIETIES OF COMPRESSION OF THE CORD

Foix and Nicolesco [29] expressed the belief that as a cause of paraplegia in flexion Pott's disease was more frequent even than extramedullary tumor. In 7 of 13 cases of spastic paraplegia in flexion due to caries of the spine collected from the literature the contracture developed early, apparently as a result of rapid compression. Flexion was said to have been noted in Ollivier's case [4] immediately after the patient fell with his legs paralyzed. In 1 each of the cases of Klippel and Monier-Vinard [30a] and Souques and Nadal [30c] a tendency to flexion was noted almost from the beginning; the tendency appeared early in Souques and Nadal's second case and in 2 of Sorrel-Dejerine's [30d] cases. Two months after an abrupt onset of flaccid paraplegia in a case reported by Cornejo Saravia and Mulcahy,[30e] the limbs became spastic and at once started to flex.

Four months after a cold abscess pointed externally in Ollivier's case the patient was able to extend his legs voluntarily and was no longer

29. Foix, C., and Nicolesco, I. C.: Valeur diagnostique et prognostique des modifications du tonus au cours des paraplégies d'origine médullaire, Paris méd. **12**:315, 1922.

30. (*a*) Klippel and Monier-Vinard: Paraplégie avec contracture en flexion et exaltation des réflexes de défense, Rev. neurol. **24**:139, 1912; (*b*) cited by Nicaud, P.: La paraplégie en flexion, Paris, Vigot Frères, 1914. (*c*) Souques and Nadal: Paraplégie en flexion avec exagération des réflexes d'automatisme médullaire, Rev. neurol. **26**:774, 1913. (*d*) Sorrel-Dejerine: Contribution à l'étude des paraplégie pottiques, Paris, Masson & Cie, 1925. (*e*) Cornejo Saravia, E., and Mulcahy, J.: Paraplejia póttica en flexión, Bol. y trab. de la Soc. de cir. de Buenos Aires **19**:853, 1935. (*f*) Souques, A.: Paraplégie pottique en flexon, Rev. neurol. **39**:649, 1923. (*g*) Lian, D. C., and Rolland, J.: Paraplégie spasmodique avec contracture en flexion (type cutanéo-réflex de Babinski) dans un mal de Pott, ibid. **23**:843, 1912.

troubled by spasmodic movements. After spontaneous rupture of an abscess in Souques' case [30f] a flexion contracture of thirty-one months' duration disappeared within two months, and there was also rapid return of power. An Albee operation was performed in Cornejo Saravia and Mulcahy's case [30e] sixteen months after onset of the paraplegia. The patient did not begin to improve until six months later, but recovered entirely from the flexion contracture in three and one-half years and was subsequently able to walk. Sorrel-Dejerine,[30d] in 5 of whose 39 cases of Pott's paraplegia there was a flexion contracture, expressed the view that completely developed paraplegia in flexion was indicative of chronicity.

A contracture in flexion had developed six weeks after onset of symptoms in Gordon's case [31] of involvement of the thoracic region of the cord by an extradural suppurative process. In an instance of compression of the dorsal portion of the cord by an aneurysm of the aorta reported by López Albo [32] involuntary flexion movements appeared as paralysis became complete, ten months after onset of weakness, and within a few months led to a contracture in flexion.

DISSEMINATED SCLEROSIS

Although he had encountered flexion contracture in cases of disseminated sclerosis, Goldflam [33] expressed the view that its presence in a doubtful case would render a diagnosis of tumor of the spinal cord more likely. Foix and Nicolesco [29] expressed the belief that paraplegia in flexion is rarely associated with disseminated sclerosis, and then as a rule only in the late stages. Ten cases in which a flexion contracture had developed were collected from the literature. The contracture was present nine months after multiple sclerosis had become manifest clinically in Cornil's case [34a] and came on in Souques' case [34b] as paralysis became complete, eighteen months after onset. In a patient seen by

31. Gordon, A.: Flexion Paralysis of Spinal and Cerebral Origin, J. Nerv. & Ment. Dis. **62**:354, 1925.

32. López Albo, W.: Compresión medular por aneurisma de la aorta torácica, An. de med. int. **4**:603, 1935.

33. Goldflam, S.: Ein Beitrag zur Semiologie des Verkürzungsreflexes, Deutsche Ztschr. f. Nervenh. **80**:238, 1924.

34. (*a*) Cornil, L.: Sclérose en placques avec paraplégie en flexion, Rev. neurol. **1**:163, 1928. (*b*) Souques, A.: Paraplégie spasmodique organique avec contracture en flexion et exagération des reflexes cutanés de défense, ibid. **21**:376, 1911. (*c*) Etienne, G., and Gelma, E.: Paraplégie spastique spinale en flexion, Nouv. iconog. de la Salpêtrière **24**:337, 1911. (*d*) Henner, K.: Myopathie Duchenne, myopathie atypique (Leyden) et paraplégie en flexion dans la même famille, Časop. lék. česk. **53**:1377, 1415 and 1451, 1924; abstracted, Rev. neurol. **2**:359, 1925. (*e*) Devic, A., and Weigert, E.: Paraplégies en flexion, J. de méd. de Lyon **16**:549, 1935.

André-Thomas [20] twenty months after recurrence of paraplegia and five months after onset of involuntary movements, the flexion contracture, though still intermittent, was tending to become permanent. In cases reported by Babinski,[8] Etienne and Gelma [34c] and Henner [34d] the patients were over 50 years of age, and the contracture had developed relatively late in the course of the disease.

A second patient with multiple sclerosis examined by Babinski [18] had an intermittent flexion contracture. Devic and Weigert,[34e] in 2 cases, and Walshe,[11] in 1 case, observed the transition from a paraplegia in extension to one in flexion. In Walshe's case the patellar and achilles reflexes disappeared from the right lower limb as it began to assume a position of flexion while the left was still rigid in extension. With progressive dissolution of reflex activity, both limbs became flaccid shortly before the patient's death. Øwre [16] stated that in the course of multiple sclerosis a passing disturbance in the general physical condition might give rise to transient paraplegia in flexion. Irritation from an infected pilonidal cyst was evidently a factor in a case of probable multiple sclerosis coming to my attention, since, according to the history, a flexion contracture of two months' duration subsided after rupture of the cyst.

MYELITIS AND ENCEPHALOMYELITIS

When acute transverse myelitis terminates in partial recovery, the sequence of events characteristic of gradually progressive lesions may be reversed; that is, early paraplegia in flexion may be succeeded by paraplegia in extension. Walshe [11] gave details of a case in which flexor reflexes demonstrated in the originally flaccid lower limbs became increasingly active, until a contracture in flexion started to develop thirteen weeks after onset. With the appearance of spasms in the extensor muscles some months later, the flexor spasms began to abate, and nine months after onset the patient had spastic paraplegia in extension. A patient with acute myelitis observed by Böhme [35] experienced a flexion contracture subsequent to the appearance of a decubitus ulcer three months after onset. The contracture was corrected by mechanical means after the ulcer healed, and the patient later presented spastic paraplegia of the ordinary type. A similar history was related by a patient with spastic paraplegia whom I examined nine years after recovery from the acute stage of postvaccinial encephalomyelitis.

In the following case flexor spasms were aggravated after the recent appearance of a trophic ulcer, and a flexion contracture developed after the patient's admission to the hospital.

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35. Böhme, A.: Untersuchungen über die koordinierte Reflexe des menschlichen Lendenmarks, besonders die rhythmischen Reflexe, Deutsche Ztschr. f. Nervenh. **56**:217, 1917.

CASE 3.—*History.*—A woman aged 22, who was registered at the Mayo Clinic on Nov. 21, 1930, began to complain of paresthesias in her trunk and limbs after an attack of influenza eight months before, and in the course of a few weeks became paralyzed in her right upper and both lower extremities. A considerable return of power three months after onset was soon followed by a relapse, and involuntary movements of flexion appeared in her lower limbs three months before admission to the clinic. Vision began to fail in the right eye a month later, and she had recently been troubled with involuntary movements in her upper, as well as in her lower, extremities. A sacral ulcer developed during the trip to Rochester; flexor spasms became more intense, and a few days after the patient's arrival passive extension of the lower limbs was no longer possible.

Examination.—The right eye was totally blind due to acute optic neuritis. The upper extremities, which showed a moderate degree of spastic weakness, flexed spasmodically at times, particularly when an effort was made to move them passively. The biceps, triceps and supinator reflexes were hyperactive, and Hoffmann's reflex was positive bilaterally. There was tremor of the hands on movement.

The lower extremities were totally paralyzed and were contracted in a position of marked flexion at the hips and knees. The abdominal muscles participated in the frequent and painful flexor spasms of the lower limbs, which could be reproduced at will by appropriate stimulation. The patellar reflexes could not be elicited, but the hamstring reflexes were moderately hyperactive and the achilles reflexes were hyperactive. The reflexes of Babinski, Chaddock, Mendel and Bechterew and Rossolimo were present on both sides. All qualities of sensation were abolished below the level of the umbilicus. The spinal fluid contained 3 small lymphocytes in a cubic millimeter and 40 mg. of total protein in a hundred cubic centimeters. The colloidal gold curve was 1212221000; Wassermann and Nonne tests yielded negative results.

Course.—On Dec. 23, 1930 paralysis of the right side of the diaphragm and signs of pneumonia were discovered. The patient died five days later; permission for autopsy was refused.

Goldflam [33] stated that he had seen flexion contracture develop in cases of disseminated encephalomyelitis, as well as in those of transverse myelitis. Flexion contracture was seen occasionally by Oppenheim [36] in the later stages of acute myelitis, but more often, in his experience, a flexed position of the lower extremities alternated with one of extension. Two patients whom I examined seven months and eight years, respectively, after onset of the contracture were still troubled with flexor spasms. Although the extensor muscles were very spastic in the second case, the limbs tended to assume a flexed position at night. Information as to the order of events was scanty in the following case, but the legs were probably spastic in extension before a flexion contracture developed.

CASE 4.—*History.*—A Negro aged 38, who was registered at the Mayo Clinic on May 4, 1931, began to drag his right leg in April 1930, after complaining

36. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1923.

for a month of pain along the right iliac crest, and awakened the morning after the onset of this trouble with both lower extremities completely paralyzed. The limbs gradually passed from a flaccid into a spastic state and, after the appearance of involuntary movements of flexion, finally contracted in a flexed position. The bowels and bladder were incontinent.

Examination.—Objective neurologic signs were limited almost entirely to the lower limbs. The lower abdominal reflexes were sluggish, but the upper abdominal reflexes were almost normally active. The lower limbs were paralyzed and contracted in a position of marked flexion, from which they could be extended to only a slight extent. All qualities of superficial sensation were diminished up to the groins, impairment being marked in both legs and the lower parts of the thighs. Vibratory sensation was moderately diminished at the left ankle but was normal elsewhere, although sense of position was impaired in the toes of each side. Reflexes of defense were pronounced. The knee and ankle jerks were moderately hyperactive, and the hamstring reflexes were slightly hyperactive. Ankle clonus was present but not sustained. The reflexes of Babinski, Chaddock, Rossolimo, Mendel and Bechterew and Oppenheim were elicited on both sides. Several ulcers, apparently of long standing, were noted on the buttocks.

The spinal fluid contained 2 lymphocytes in a cubic millimeter, a small amount of globulin and 50 mg. of total protein in a hundred cubic centimeters; the Wassermann reaction was negative; the colloidal gold curve was 3322310000. Queckenstedt's test showed no blocking of the subarachnoid space.

SUBACUTE COMBINED DEGENERATION OF THE CORD

The first report of a case of subacute combined degeneration with flexion contracture that could be found in the literature was one by de Jong [37a] in 1927. Hall and Hirsch [37b] reported a case in which the contracture appears to have developed rapidly as weakness of the legs became aggravated. The contracture was a terminal event in Hassin's [37c] case; flexor reflexes had been elicited when the patient entered the hospital three weeks before, but at that time paralysis of the lower limbs was not complete. The diagnosis of subacute combined degeneration was confirmed by postmortem study in all 3 of these cases. Hyland and Farquharson [37d] saw flexion contracture develop in 3 of 74 consecutive cases of subacute combined degeneration with pernicious anemia. In a case reported by Moersch and Pfeffer,[37e] one of a pair of identical twins suffering from pernicious anemia and subacute combined degeneration

37. (*a*) de Jong, H.: Un cas de sclérose combinée dans l'anémie pernicieuse avec polynévrite présentant les symptômes d'une "paraplégie des vieillards," Acta psychiat. et neurol. **2**:105, 1927. (*b*) Hall, G. W., and Hirsch, E. F.: Paraplegia in Flexion with Subacute Combined Sclerosis of the Cord, Arch. Neurol. & Psychiat. **23**:257 (Feb.) 1930. (*c*) Hassin, G. B.: Paraplegia in Flexion and Symptom of Lhermitte, ibid. **29**:855 (April) 1933. (*d*) Hyland, H. H., and Farquharson, R. F.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, ibid. **36**:1166 (Dec.) 1936. (*e*) Moersch, F. P., and Pfeffer, T. J.: Subacute Combined Degeneration of the Spinal Cord Affecting Twins, J. Iowa M. Soc. **22**:221, 1932.

had paraplegia in flexion. In the case to be described flexor spasms followed the appearance of a decubitus ulcer and led five months later to development of a severe contracture.

CASE 5.—*History.*—In a man aged 46, who was registered at the Mayo Clinic on July 8, 1930, an ataxic gait and paresthesias of the lower extremities were first noticed in April 1929, after an illness with influenza. A diagnosis of pernicious anemia was made in the following November, and a month after this increasing weakness and unsteadiness of the lower limbs prevented the patient from walking. He consumed 1 pound (453 Gm.) of liver every day during January 1930, and at this time had a second attack of influenza, which kept him in bed for seven weeks. A decubitus ulcer developed soon after the onset of this illness, and a short time later the patient began to be troubled with involuntary jerking of the lower extremities. Control of the sphincters was lost in February. The following May, about two months before admission, the lower limbs "tightened up" and quickly assumed a permanently flexed position.

Examination.—The patient lay in bed with the thighs in contact with the abdomen, the calves touching the thighs and the feet somewhat dorsiflexed. The abdominal muscles were tightly contracted. The receptive zone for the flexor reflex extended from the feet to the level of the umbilicus. The patellar reflexes were hypoactive, while the hamstring and achilles reflexes were normally active. Babinski's reflex was present bilaterally. Vibratory sensation was abolished over the ankles and tibial tubercles, and the sense of position was lost in the toes. Superficial sensation was moderately diminished as high as the iliac crests, impairment being somewhat more pronounced below the knees. An ulcer over the sacrum appeared to be healing.

. The gastric contents contained no free hydrochloric acid. The concentration of hemoglobin in the blood was 68 per cent; the red cells numbered 3,500,000 and the white cells 5,200 in a cubic millimeter. Morphologic changes in the blood cells were not particularly characteristic of pernicious anemia. The patient was discharged on July 21, 1930, with instructions to eat 1½ pounds (680 Gm.) of liver each day.

Course.—On Aug. 4, 1931 the patient wrote that his spasms were less marked, although he had not taken liver since the preceding November. In a letter dated July 3, 1933 it was stated that the patient had died.

OTHER DISEASES OF THE SPINAL CORD

Foix and Nicolesco [29] expressed the view that flexion contracture should be rare in cases of syphilis of the spinal cord since reflexes of defense are not active as a rule in that condition. The contracture was apparently relieved by antisyphilitic treatment in a case reported by Marinesco and Paulian.[38] Examination of the spinal fluid in this case showed pleocytosis and a positive reaction for globulin, but the Wassermann reaction was not mentioned. A case of Friedreich's ataxia with a flexion contracture and the synkinesias of spinal automatism was

38. Marinesco, G., and Paulian, D.: Un cas de paraplégie avec contracture en flexion presque complètement guéri par le traitement spécifique, Rev. neurol. **39**:663, 1923.

reported by Jedlicka and Henner.[39] In 1 of Ollivier's [4] cases of paraplegia in flexion the clinical and pathologic findings were strongly suggestive of syringomyelia. Painful spasms of the lower limbs led to development of a flexion contracture in a case of amyotrophic lateral sclerosis with terminal bulbar involvement reported by Anglada.[40] Flexion contracture was a prominent feature in cases of senile paraplegias of spinal origin studied by Démange [41] and Lhermitte.[1]

TRAUMATIC LESIONS OF THE CORD

Development of a spastic contracture following total section of the cord above the lumbar enlargement is rare for two principal reasons: First, injury to the isolated segments resulting from indirect damage, toxemia and so-called isolation dystrophy is often severe enough to preclude any considerable recovery of reflex activity; second, in cases of other injuries either the return of such activity is checked rather early or the proprioceptive reflexes fail to keep pace with the active flexor reflex. In a case of fracture of the spine with signs of a transverse lesion at the tenth dorsal segment reported by Schultze,[5] "cutaneous reflexes" were greatly exaggerated when the patient was examined four months after injury. A flexion contracture developed within the next few months. Since at autopsy the pointed ends of the cord were observed to be connected only by scar tissue and both ascending and descending degeneration was demonstrated, the transverse lesion would seem to have been complete. Kausch [42] reported a case of complete section which occurred accidentally during an operation for the relief of compression at the ninth and tenth dorsal segments. Although the lower limbs, previously spastic, were entirely flaccid immediately after operation, the knee and ankle jerks returned after twenty-two hours. A withdrawal reaction was demonstrated twenty-four hours later, and by the sixth day there was a marked flexion contracture.

Riddoch [13] in his cases of complete division of the thoracic part of the cord by a gunshot wound found that reflex activity and tone

39. Jedlicka, V., and Henner, K.: Friedreich's Ataxia with Flexion Paraplegia and Another Case with Loss of Vestibular Sensation, Časop. lék. česk. **64**:1396, 1925.

40. Anglada: Sclérose latérale amyotrophique ascendante avec manifestations douloureuses et paraplégie en flexion intense, Montpellier méd. **33**:73 and 97, 1911; abstracted, Rev. neurol. **23**:261, 1912.

41. Démange, E.: De la contracture tabétique progressive en sclérose diffuse d'origine vasculaire simulant la sclérose fasciculée, observée chez les vieillards athéromateux, Rev. de méd. **5**:545, 1885.

42. Kausch: Ueber das Verhalten der Sehnenreflexe bei totaler Querschnittsunterbrechung des Rückenmarks, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **7**:541, 1901.

appeared earlier and remained more marked in the flexor than in the extensor muscles. When the general physical condition declined as a result of sepsis or intercurrent infection the extensor muscles were the first to become flaccid. The patients lay, during the stage of reflex activity, with the limbs slightly flexed at the hips and knees, the thighs somewhat adducted and externally rotated and the feet and toes dorsiflexed. "From the reflex point of view," Riddoch wrote, "the clinical picture found in cases of complete transection of the cord resembles that described as 'paraplegia in flexion' by Babinski and Walshe." In a later paper, Riddoch [19] stated that flexion contracture might develop unless suitable precautions were taken. Cassirer,[43a] in reporting an analysis of 184 injuries to the spinal cord observed during the World War, mentioned a few cases of severe flexion contracture under the heading of partial transverse lesions. In the discussion of this report Mann [43b] expressed the view that a contracture of this type was more typical of incomplete than of total section. Foerster,[43c] however, said he had seen outspoken spastic contracture of the flexor muscles in 3 cases of anatomically verified total transverse lesion.

Foerster [15] was able, through careful immobilization of the limbs, to induce contracture of the extensor muscles in 2 cases of complete transection. He regarded these as rare exceptions to the general rule that spastic contracture, when it does occur in total section, is almost invariably one in flexion. In a remarkable case reported by Cadwalader [44] the lower extremities were usually held in a position of partial flexion, but transient hypertonus of the quadriceps femoris muscle could be induced by passive extension of the knee (shortening reaction). Riddoch [13] found some indication of a crossed extensor response in 2 cases of total division of the cord, but was never able to elicit an extensor reflex from stimulation of the upper part of the thigh or the perineal region. Foerster demonstrated extensor reflexes in the 2 cases previously referred to, but even here he was unable to convince himself that the flexor response was followed by active contraction of the extensor muscles.

A young man whom I examined eighteen months after he had received a compression fracture of the cervical part of the spine had an intermittent type of flexion contracture. Although sensation and volun-

43. (*a*) Cassirer, R.: Zur Klinik der traumatischen Schädigungen des Rückenmarks, Ztschr. f. d. ges. Neurol. u. Psychiat. **70**:110, 1921. (*b*) Mann, L., in discussion on Cassirer: Deutsche Ztschr. f. Nervenh. **70**:47, 1921. (*c*) Foerster, O., in discussion on Cassirer: ibid. **70**:38, 1921.

44. Cadwalader, W. B.: Report of the Condition of a Case of Complete Division of the Spinal Cord by Gunshot Wound Nineteen Years After the Injury, Ann. Surg. **71**:719, 1920.

tary power were lost below the seventh cervical segment, the hyperactive knee and ankle jerks and the subsequent development of patellar and ankle clonus along with involuntary movements of extension [45] were in keeping with an incomplete transverse lesion. Extensor reflexes predominate in the usual case of partial section but, as Riddoch [13] remarked, prespinal arcs may on occasion be so gravely injured that the clinical picture is more suggestive of total section.

LESIONS OF THE BRAIN STEM

A tumor lying to the right of the pons and medulla oblongata and causing considerable compression of these structures was observed at autopsy in 1 of the cases reported by Babinski [8] in 1899. The legs were growing weaker about the time the patient became blind from secondary optic atrophy; involuntary movements of flexion came on shortly thereafter, and a flexion contracture developed within the next few months. Progressive spastic paraplegia, terminating in a flexion contracture a year after onset, was associated with Parkinson's syndrome and paralysis of upward gaze in a patient observed by Bouttier, Alajouanine and Girot.[46] The authors expressed the view that the pyramidal tracts were involved in an encephalitic process at some point above the pons, possibly at the level of the midbrain.

CEREBRAL LESIONS

Charcot [47] stated that in cases of hemiplegia development of a flexion contracture, first in the paralyzed lower limb and subsequently in the opposite member, was fortunately a rare occurrence. In cases of a similar train of events reported by Dèmange [6] and Herman,[48] extensive cerebral damage, arteriosclerotic in origin, was observed at autopsy. Vincent, Krebs and Chavany [49] observed 2 cases of hemiplegia due to unilateral cerebral softening in which the flexed lower extremities could be passively extended, though with considerable difficulty, on the paralyzed side. The authors attributed the withdrawal movements they observed to "hyperalgesic reflexes" and expressed the view that they were not analogous to reflexes of defense.

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45. Dr. C. Van Epps, of Iowa City, and the patient himself gave me this additional information.

46. Bouttier, H.; Alajouanine, and Girot: Paraplégie en flexion avec état Parkinsonien et syndrome de Perinaud, Rev. neurol. **38**:1514, 1922.

47. Charcot, J. M.: Leçons sur les localizations dans les maladies du cerveau et de la moelle épinière, Paris, A. Delahaye et Lecrosnier, 1876-1880.

48. Herman, W.: A Case of Paraplegia in Flexion of Arteriosclerotic Origin, Psychiat. en neurol. bl. **30**:32, 1926.

49. Vincent, C.; Krebs, and Chavany, J. A.: Pseudo-paraplégie en flexion par lésion cérébrale unilatérale, Rev. neurol. **1**:337, 1925.

Lejonne and Lhermitte [50] stated that in senile paraplegias due to extensive bilateral lacunar degeneration flexion contracture supervened when the patient survived the stage of complete paralysis of the lower limbs, dementia and trophic ulceration. Three years after reporting 2 cases of pseudobulbar palsy in which paraplegia in flexion was a late development, Alajouanine published his observations in 40 cases of a similar nature.[51] Evolution of the pseudobulbar palsy was usually insidious, that is, without evidence of vascular accidents, and was accompanied by progressive dementia. Changes in the reflexes characteristic of pyramidal involvement were lacking at times even when reflexes of defense were becoming active. The contracture in flexion was always intermittent at first, and in some instances flexor spasms either failed to appear until shortly before death or persisted for several years without development of a contracture. Aside from the absence of anesthesia, these cases differed mainly from those of spinal paraplegia in flexion in that one limb was flexed more than the other and involuntary movements ceased after the contracture was established. As in the cases of Dèmange and Herman, the essential pathologic lesion was an extensive bilateral lacunar degeneration of the centrum semiovale and basal nuclei, with atrophy of the corpus callosum.

Active reflexes of defense, a crossed extensor reflex and a flexion contracture of long standing were observed by Marie and Foix [52] in a mentally deteriorated woman, aged 70. Postmortem study revealed marked atrophy of the corpus callosum, particularly in its middle portion, and subependymal necrosis in the superior and outer walls of the lateral ventricles with degeneration of projection fibers from the paracentral gyri. A case studied by Verhaart [53a] was similar, clinically and anatomically, to those reported by Alajouanine; cases of the same order have been reported by Ley and van Bogaert.[53b] Pseudobulbar palsy, reflexes of defense, cogwheel rigidity and late development of a flexion contracture were prominent features in cases of epilepsy with dementia and progressive neurologic changes reported by Hodskins

50. Lejonne, P., and Lhermitte, J.: Les paraplégies d'origine lacunaire et d'origine myélopathique chez les vieillards, Arch. gén. de méd. **196**:3009 and 3073, 1905.

51. Alajouanine, T.: (*a*) Sur un type de paraplégie en flexion d'origine cérébrale, Ann. de méd. **13**:243, 1923; (*b*) La paraplégie en flexion terminale des pseudobulbaires, Paris méd. **2**:266, 1926.

52. Marie, P., and Foix, C.: Paraplégie en flexion d'origine cérébrale par nécrose sous-épendymaire progressive, Rev. neurol. **36**:1, 1920.

53. (*a*) Verhaart, W. J. C.: "Paraplégie en Flexion" in Consequence of Decerebration Above Nucleus Ruber, Psychiat. en neurol. bl. **34**:33, 1930. (*b*) Ley, R., and van Bogaert, L.: Contribution à la connaisance de la paraplégie en flexion, type Babinski, d'origine cérébrale, J. de neurol. et de psychiat. **26**:547, 1926; cited by Verhaart.

and Yakovlev.[54] In 2 cases in which autopsy was performed chronic degenerative changes were especially intense in the globus pallidus, pedunculohypothalamic formations and the cortex of the frontal lobes.[54b] Contrary to the condition in the usual case of paraplegia in flexion, Hodskins and Yakovlev's patients retained some degree of voluntary control until tendinous retraction set in. Marie and Foix's patient was also said to exhibit a certain amount of voluntary movement in her lower limbs.

CASE 6.—*History.*—A woman aged 68, who was first seen in a nursing home on June 25, 1938, had had a stroke ten years before, another four years later and three more in the past three years. Relatives were not clear as to which side of the body was affected in these various accidents, but were certain that each side had been involved on one occasion or another. Speech and swallowing were impaired after the second ictus, and for the past three years the patient had been forgetful, somewhat childish and subject to spasmodic laughing and crying. She had been completely disoriented and disturbed mentally since a sixth attack of hemiplegia, which involved the right side, four weeks before. Although voluntary control quickly returned to the right side of the face and right arm, the last accident had been followed almost immediately by flexor spasms of the lower limbs, which soon assumed a permanently flexed position. The patient had been completely incontinent for the past four weeks.

Examination.—The patient was poorly nourished, restless and entirely uncooperative; speech was unintelligible. The face was more or less without expression, and the lips responded to stroking with a typical sucking movement. Moderate spasticity with hyperactivity of the tendon reflexes and a bilaterally positive Hoffmann reflex were noted in the upper extremities. The retinal arteries and those of the extremities were sclerotic.

The lower limbs were in a position of marked flexion at the hips and knees, with the thighs adducted and the feet slightly flexed in the plantar position. Passive extension was possible only to a limited extent and was productive of considerable pain. The abdominal muscles were tightly contracted and participated in the flexor reflex, which could be elicited with nocuous stimulation at any point below the groins. Pinching the skin of the lower part of the abdomen, however, was followed by contraction of the ipsilateral abdominal muscles only. Flexion of either lower limb in response to forced flexion of the toes (Marie-Foix maneuver) was followed after a short interval by beginning contralateral extension, which was quickly succeeded by more prolonged flexion of the opposite member. Flexion of the left limb in response to stimulation of the foot was often accompanied by ankle clonus, but if stimulation was continued the foot soon assumed a position of dorsiflexion and the clonus ceased. The hamstring reflexes were moderately hyperactive, as were the right patellar and achilles reflexes. Ankle clonus was elicited by percussion of the left achilles tendon, while the left patellar reflex was somewhat less hyperactive than the right. The reflexes of Babinski, Chaddock, Rossolimo and Mendel and Bechterew were demonstrated on both sides. Though the mental state precluded a proper test, sensation seemed to be preserved.

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54. Hodskins, M. B., and Yakovlev, P. I.: (*a*) Neurosomatic Deterioration in Epilepsy, Arch. Neurol. & Psychiat. **23**:986 (May) 1930; (*b*) **27**:113 (Jan.) 1932.

Course.—When the patient was seen on July 14, 1938, a superficial ulcer was present over the sacrum, and the upper as well as the lower extremities were tightly contracted in a flexed position. The patient groaned on being touched. The disturbed state gradually came to be replaced by one of apathy in the ensuing weeks, until even the flexor responses ceased to be painful. Although the patient moved her upper limbs little, they became less spastic, and at times flexion of the thighs and contraction of the abdominal muscles were not marked. The hamstring muscles, however, remained spastic, and when the patient subsequently became less apathetic flexion of the thighs increased again. Involuntary movements of flexion were rarely noted, but slight abduction of the thighs, apparently involuntary, was observed on a number of occasions.

On examination, on Sept. 11, 1938, the right ankle jerk was unobtainable and both knee jerks were sluggish, but the hamstring reflexes were still brisk and ankle clonus was elicited on the left side. Although the patient seemed moribund when examined on Oct. 9, 1938 and the withdrawal reaction was feeble, the condition of the tendon reflexes was practically unchanged. A few hours before death on the following day, the right lower limb could be almost completely extended and it was possible to extend the left lower limb to a considerable degree. The hamstring and left achilles reflexes still gave some indication of their former activity, and even a sluggish patellar response was obtained on either side. Efforts to obtain permission for an autopsy were unsuccessful.

Foerster [55] stated that in cases of spastic paraplegia due to bilateral traumatic lesions of the motor cortex he had "repeatedly" seen an original paraplegia in extension transformed into one in flexion through the influence of continuous stimulation from wounds and ulcers of the lower extremities, and that after healing of the wounds and ulcers the limbs returned to the extended position. Morelli and Quagliotti [56] observed the development of flexion contracture in a case of epidemic encephalitis. About a week after recovery from the lethargic stage hemiplegia supervened and was followed in a few days by flexion of the paralyzed lower limb. The other lower extremity became weak and began to flex at the same time, but, unlike the opposite member, never assumed a posture of extreme flexion. Lively withdrawal reflexes and some of the features of parkinsonism were noted.

Little and Freud [57] both noted flexion contractures of the lower limbs in cases of spastic diplegia in children. Outspoken flexion contracture is not uncommon, according to Foerster,[55] in association with congenital and infantile paraplegias and diplegias of cerebral origin,

55. Foerster, O.: Symptomatologie der Erkrankungen des Grosshirns, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, pp. 1-357.

56. Morelli, J. B., and Quagliotti: Paraplégie en flexion, An. de Fac. de med., Montevideo **14**:1138, 1929.

57. Little, W. J.: On the Influence of Abnormal Parturition, Difficult Labours, Premature Birth and Asphyxia Neonatorum on the Mental and Physical Condition of the Child, Especially in Relation to Deformities, Tr. Obst. Soc., London **3**:293, 1862. Freud, S.: Zur Kenntnis der cerebralen Diplegien des Kindesalters, Vienna, Franz Deuticke, 1893.

but with increasing age the extensor muscles become stronger and the lower limbs eventually assume a position midway between flexion and extension. In a case of congenital syphilis with mental deterioration reported by Noica and Gracium [58a] progressive paraplegia of cerebral origin terminated in a flexion contracture. The contracture came on early in a case of probable encephalitis complicating whooping cough reported by Pichon and Cambéssedes.[58b] In neither of these cases could reflexes of defense be elicited.

TREATMENT

Øwre [16] advised stretching a sheet across the patient's limbs to prevent a possible contracture in cases in which involuntary movements of flexion were active. Plaster casts must be applied with meticulous care, since irritation of the skin will only aggravate the spasms and thus increase the patient's suffering. Hyland and Farquharson [37d] finally succeeded in overcoming marked flexion contracture in 2 of 3 cases of subacute combined degeneration. Large amounts of liver extract were given parenterally, and the limbs were immobilized in plaster casts in the intervals between repeated manipulations, with the patients under anesthesia. These authors warned against the use of traction by means of adhesive strips, a point no doubt well taken in view of the resulting ulceration which necessitated amputation in 1 of Souques and Nadal's cases.[30c] In other cases of subacute combined degeneration Hyland and Farquharson found that mild contractures were easily corrected by giving adequate amounts of liver and daily stretching of the limbs. In the case of Schaller and Gilman [22d] the contracture subsided to a degree permitting the use of braces after removal of an extramedullary tumor.

Unless the causative lesion subsides spontaneously or is relieved by appropriate treatment, attempts at correcting a marked contracture in flexion by mechanical methods are often futile, though such treatment combined with removal of sources of irritation seems to be successful on occasion.[35] Marie, Bouttier and Pierre [59] reported temporary relief of flexion contracture following intramuscular injection of cicutine hydrobromide in doses of from 1 to 3 mg. Section of the posterior lumbosacral roots will relieve the contracture, but will not necessarily check the involuntary movements if the causative lesion is situated at some dis-

58. (*a*) Noica, D., and Gracium, E.: Paraplégie spasmodique avec troubles cérébraux d'origine hérédo-syphilitique, Arch. de méd. d. enf. **37**:1, 1934. (*b*) Pichon, E., and Cambéssedes, H.: Sur un cas de paraplégie en flexion due probablement à un processus infectieux aigu d'origine coquelucheuse chez une enfant de trois ans, ibid. **37**:33, 1934.

59. Marie, P.; Bouttier, H., and Pierre, J. R.: L'action de bromhydrate de cicutine sur les paraplégies en flexion et sur l'automatisme médullaire, Rev. neurol. **37**:841, 1921.

tance above the first lumbar segment. Forester [15] asserted that if these movements are to be entirely and permanently checked in such cases, the posterior and anterolateral columns of the cord must also be sectioned.

COMMENT

Riddoch,[13] on the basis of his experience with transection of the cord, concluded that the neuromuscular mechanism of flexion was purely spinal in man, as well as in lower animals, and was independent of higher control so far as its purely protective reflex activities were concerned. He also expressed the view that with incomplete lesions of the cord propriospinal pathways and paths from the pons and midbrain maintained postural tone in the extensor muscles and inhibited the spread of impulses, leading to exaggerated movements of flexion. The extensor reflexes are dependent to some extent on prespinal connections, even in lower animals,[60] but in man this dependence appears to be still greater. Cases have been reported,[61] nevertheless, in which, despite complete or almost complete transverse destruction of the cord by gradual compression, spastic paraplegia in extension persisted until death. Observations of this kind, indicating as they do the existence within the cord of mechanisms capable of maintaing exaggeration of the extensor reflexes, suggest that prespinal connections serve mainly to inhibit the flexor reflexes.

That depression of extensor reflexes is not entirely a matter of reciprocal inhibition would be indicated, however, by the relative flaccidity of the extensor muscles in certain cases at a time when the flexor reflexes had not been enhanced to a degree sufficient to bring about a contracture (case 2). In a patient with an intermittent flexion contracture examined by Babinski [18] the patellar and achilles reflexes were sluggish even when the limbs were extended. Reflex excitability of the extensor muscles may be poorly sustained, furthermore, in cases of extensive transverse lesion of the cord without flexion contracture. It seems likely, therefore, that at least some of the arcs for extensor reflexes extend above spinal levels.

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60. Sherrington, C. S.: Remarks on the Reflex Mechanism of the Step, Brain **33**:1, 1910.

61. (*a*) Schultze, F.: Ein Fall von perimeningealem Tumor mit completem Druckschwund des unteren Halstheils des Rückenmarks, Arch. f. Psychiat. **11**:770, 1881. (*b*) Brissaud, E., and Feindel: Paraplégie spasmodique dans un cas de compression de la moelle dorsale équivalent à une section, Rev. neurol. **9**:822, 1901. (*c*) Hirtz, E., and Delamère, G.: Compression de la moelle dorsale par un endothéliome, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:308, 1902. (*d*) Souques and Blamoutier: Paraplégie spasmodique permanent malgré la destruction de la moelle dorsale par une tumeur, Rev. neurol. **31**:300, 1924. (*e*) Raymond and Cestan.[25c]

When an acute transverse lesion is reversible to some degree, prespinal connections may be reestablished, with resulting conversion of early paraplegia in flexion to one in extension, as in Walshe's case [11] of acute myelitis. Since descending pathways from supraspinal and subcortical centers are more widely scattered in the lateral and anterior columns of the cord than are the pyramidal tracts,[62] they are probably less vulnerable. Foerster [15] suggested that the pyramidal tracts are more vulnerable because they are phylogenetically younger. In any event, signs of pyramidal involvement appear relatively early in association with progressive lesions, whereas release of flexor reflexes to a degree sufficient to produce a contracture generally occurs only after paralysis has become complete. Foerster's experience [55] with excision of the motor cortex in man would indicate that, in addition to the pyramidal tracts, other descending pathways must be involved by the time all voluntary control is lost.

Earlier writers were inclined to attribute the establishment of a permanent contracture in flexion to fibrous retraction.[63] Acceptance of such an explanation would be to ignore entirely the obviously active nature of the process, to say nothing of cases in which a contracture of some standing subsided spontaneously. While admitting that fibrous retraction did occur, Foerster [15] stated he had "ever and again" been surprised at the ease with which the limbs could be straightened by mechanical means after section of posterior spinal roots, whereas, without this operative procedure mechanical straightening was difficult, if not impossible. Böhme [12] attributed fixation of the limbs to continuous flexor reflexes with simultaneous weakening of the extensor reflexes, while Foix [27] and Fleischmann [64] both ascribed it to fixation of the withdrawal reaction. As a matter of fact, the flexor reflex does not cease to be phasic after the contracture is established, as otherwise the involuntary movements of flexion would cease.

According to Foerster,[15] the contracture develops in the following manner: Through the continuous flow of afferent impulses into the lumbosacral portion of the cord and the resulting stream of motor discharges to the flexor muscles, the limbs are repeatedly brought into a flexed position. The "kinetic flexor reflex" is joined by a "postkinetic fixation reflex" (shortening reaction), which tends to persist for considerable periods. Through the almost unbroken approximation of the

62. Papez, J. W.: Reticulospinal Tracts in the Cat, J. Comp. Neurol. **41**:365, 1926.

63. Noïca, M.: A propos de l'article de M. Babinski "Paralysie spasmodique organique avec contracture en flexion et contractions involuntaires," Rev. neurol. **19**:173, 1911.

64. Fleischmann, P.: Die Abwehrreflexe und ihre Bedeutung, Arch. f. Psychiat. **80**:377, 1927.

points of insertion of the flexor muscles which results, the stretch reflex becomes enhanced to the degree that the limbs are permanently fixed in the flexed position. In regard to his observations of the crossed extensor response, Sherrington [65] wrote: " . . . in the muscle with its afferent nerve intact a proprioceptive autogenous reflex adds itself to reflexes caused by extrinsic afferents." He also found that the shortening reaction when engrafted on an active reflex contraction was more pronounced than when induced by passive approximation of the insertion points of the given muscle. Though similar investigations of the flexor reflex seem to be lacking, Sherrington's observations indicate that kinetic reflexes have a facilitating effect on static reflexes.

In reference to the stretch reflex, Fulton [66] stated that in a dog or cat sustained contraction was not seen on stretching a flexor muscle. Dusser de Barenne and Koskoff [67] were able to produce flexor rigidity of the hindlimbs in cats by transection of the bulb after decerebrate rigidity had been established by intercollicular section. When the rigidity of the flexor muscles was not maximal it could be rendered so by transection of the first lumbar segment. Since the flexor rigidity was markedly depressed by skinning of the hindlimbs and abolished by section of posterior spinal roots, stimuli essential for its existence seemed to be in part exteroceptive and in part proprioceptive. Although this state of flexor rigidity was not comparable in certain respects with the flexion contracture observed in man, it furnished a striking illustration of the experimental production of a condition somewhat similar to the latter through a release of spinal reflexes.

Böhme [12] expressed the view that the fixation reflex, though an element in spastic contracture of the extensor muscles, was not a property of the flexors. Foerster [68] was able, however, both by palpation and by the use of an action current in cases of spastic paralysis, to demonstrate an active contraction of the flexor muscles of the hip as their points of insertion were approximated. After overcoming the resistance of the vastus cruris muscles and flexing the knee in cases of spastic paraplegia, I have noted definite resistance of the hamstring muscles to passive extension, a resistance, moreover, which suddenly gave way as extension was continued (lengthening reaction).

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65. Sherrington, C. S.: On Plastic Tonus and Proprioceptive Reflexes, Quart. J. Exper. Physiol. **2**:109, 1909.

66. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

67. Dusser de Barenne, J. G., and Koskoff, Y. D.: Flexor Rigidity of the Hind Legs and Priapism in the "Secondary" Spinal Preparation of the Male Cat, Am. J. Physiol. **102**:75, 1932.

68. Foerster, O.: Schlaffe und spastische Lähmung, in Bethe, A., and von Bergmann, G.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, pp. 893-972.

Foerster,[15] as previously stated, has demonstrated by means of an action current exaggeration of the stretch reflex in the flexor muscles of patients with paraplegia in flexion. Sherrington's conclusion that reflex maintenance of posture is a chief portion of the work of the proprioceptive system applied, furthermore, to an attitude of flexion as well as to one of extension.[69]

Although Foerster has for years stressed the importance of the habitual position of the patient's limbs in determining the type of contracture,[9] he expressed recognition of the part played by reflex patterns.[15] He referred, in this connection, to cases of long-standing spastic paraplegia in which irritation from some source, such as a bed sore, so enhanced the flexor reflexes, with consequent depression of the extensor reflexes, that a contracture in flexion followed. This can happen, according to Foerster, even when connections with higher levels have been retained to such a degree as to keep the extensor muscles in a spastic state under ordinary conditions; irritation, for instance, from an anal fissure, an infected bladder or a subungual abscess may still bring about a flexion contracture which will subside once the source of irritation has been removed. Frequent induction of the fixation reflex by the active flexor reflex, in this type of case at least, would seem to be more effective in maintaining the contracture than prolonged approximation of the insertion points of the flexor muscles.

It must be admitted that in some instances healing of a trophic ulcer is attributable, in part, to improvement of the condition within the cord, which of itself might account for subsidence of the contracture. Conversely, it is also true that ulceration may be associated with progression of the underlying disease. The importance of peripheral irritation appears, nevertheless, to be well established. Indeed, it may be said with reference to certain writers,[70] who hold, in a measure, to Babinski's [8] original view regarding irritation by the causative lesion of descending tracts, that the only effective irritation is probably peripheral.

In producing spastic contractures of the extensor muscles by immobilization of the limbs in cases of complete transection of the cord, Foerster [15] made a good case for the importance of approximation of the insertion points of muscles in determining the distribution of spasticity. Persistence of a spastic contracture in extension despite practically complete anatomic division of the cord by slow compression [71] might be accounted for in this manner. During the long period that the patients referred to lay in bed with their limbs outstretched

69. Sherrington, C. S.: Postural Activity of Nerve and Muscle, Brain **38**:191, 1915.

70. Foix.[27] Devic and Weigert.[34e]

71. Raymond and Cestan.[25c] Footnote 61.

the extensor reflexes appear to have been so effectively *gebahnt* that even irritation from decutitus ulcers failed to change the type of contracture. Böhme [35] attributed continued extension of the limbs in instances of this sort to fibrous retraction, but this seems unlikely in view of the active involuntary movements of flexion described in 3 of the cases cited.[72] Since in Senator's case [25b] of division of the cervical portion of the cord by a tumor a flexion contracture developed after more than eight years of complete paraplegia, there may have been a similar development in the other cases had the patients lived longer.

The question as to the specific tracts other than the pyramidal which must be involved before a flexion contracture can develop has yet to be answered. Liddell and his associates,[73] working with cats, arrived at the following conclusion:

> The enhancement of the flexor reflex in decerebrate preparations resulting from total spinal section is due, in fact, to transection of two susceptible ipsilateral areas, the postero-lateral and the anterior. The tract in the postero-lateral region is probably the lateral reticulo-spinal tract, and in the anterior region, the vestibulo-spinal and ventral and medial reticulo-spinal tracts are probably chiefly concerned.

Fulton [66] stated that for maintenance of the extended position of the hindlimbs with experimental lesions of the cord either the pyramidal or the vestibulospinal tracts must be spared.

Babinski,[8] in a case of multiple sclerosis with flexion contracture, found that the lesions within the cord were limited largely to the anterolateral areas; the changes were less intense in the portions of the few larger plaques which extended into the posterolateral columns. Sections of the cord in cases of subacute combined degeneration illustrated in the papers of Hassin [37c] and of Hall and Hirsch,[37b] on the other hand, showed little involvement of the anterior columns. This was also true of Jedlicka and Henner's case of Friedreich's ataxia.[39] The lateral reticulospinal tracts, however, may well have been involved in these cases. It would appear from the tabulated results of Liddell and his co-workers [73] that transection of the posterolateral area releases flexor reflexes to a greater degree than does section of anterior areas. It must be emphasized, furthermore, that loss of function and demonstrable morphologic change do not always go hand in hand. Holmes [74] showed that, so far as compression of the cord is concerned, secondary degeneration might not be demonstrable even when there had been great loss of movement and sensation for a considerable time before death.

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72. Schultze.[61a] Hirtz and Delamère.[61c] Souques and Blamoutier.[61d]

73. Liddell, E. G. T.; Matthes, K.; Oldberg, E., and Ruch, T. C.: Reflex Release of Flexor Muscles by Spinal Section, Brain **55**:239, 1932.

74. Holmes, G.: On the Relation Between Loss of Function and Structural Changes in Focal Lesions of the Central Nervous System with Especial Reference to Secondary Degeneration, Brain **29**:514, 1906.

Clinical evidence suggests that in the damaged cord certain extraneous factors, i. e., depression of the extensor reflexes by some disturbance in the general condition and enhancement of the flexor reflex as a result of peripheral irritation, may have the functional effect of a more extensive anatomic lesion. Two facts seem well established: First, the more complete the transverse interruption of conduction in progressive lesions of the spinal cord, the more likely is a flexion contracture to develop; second, when reflexes return after complete transection they behave in a manner more or less characteristic of the usual case of paraplegia in flexion, and if a spastic contracture develops it is generally one in flexion. Once the latter fact is conceded, objections to the principle of spinal automatism [37c] lose much of their weight. It has been asserted recently that current views are based largely on physiologic concepts and lack anatomic confirmation,[75] and that destruction of the cord to a degree amounting to complete section has yet to be demonstrated in a case of paraplegia in flexion.[34e] Observations in the cases of Kausch [42] and Gerhardt [25a] should be sufficient to dispose of both contentions. Through a surgical mishap in the first instance the compressed portion of the cord was actually removed; in the second case the cord had been reduced at the site of compression to a transparent band devoid of conducting elements.

It is possible that in some cases of cerebral paraplegia flexion contracture occurs without preliminary exaggeration of the flexor reflexes, but this is certainly not true of the great majority. Marie and Foix [52] found the midbrain and pons intact in their case of subependymal necrosis. They expressed the view that in cases of supraspinal lesions mesencephalic involvement is not essential for release of spinal automatism and development of a flexion contracture. Alajouanine [51a] found that flexor reflexes could be released in dogs by ablation of both paracentral gyri, while Foerster [55] observed the same phenomenon in man after injury to these areas. Foerster ascribed the tendency for the stretch reflex to remain exaggerated in the extensor muscles in such cases to the influence of subcortical centers, as well as to the habitual position of the lower limbs. Foerster's observations also indicated that a continuous stream of nocuous stimuli from ulcers or wounds of the lower extremities has an effect similar to that observed with spinal lesions.

Alajouanine [51a] attributed release of the flexor reflexes in his cases of pseudobulbar palsy primarily to bilateral involvement of the pyramidal tracts. He hastened to add, however, that the reflexes had been progressively enhanced as a result of widespread cerebral disintegration.

75. Alfano, V.: Sulla paraplegia spastica con contrattura in flessióne, Ann. di med. nav. e colon. **1**:311, 1937.

Projections from extrapyramidal motor areas of the cortex could hardly have escaped serious damage in these cases. It is also unlikely that the pyramidal area (area 4) was alone involved in the cases of lesions of the paracentral gyri previously referred to. Verhaart [53a] expressed the belief that degeneration of the precentral cortex and frontal convolutions was the essential lesion in cerebral paraplegia in flexion. Alajouanine expressed the view that degeneration of the basal nuclei in his cases may possibly have helped to fix the limbs in the flexed position. A generalized attitude of flexion observed by Hodskins and Yakovlev [54] in cases of epilepsy with neurosomatic deterioration may well have been due to changes in the globus pallidus and related structures. In patients with marked paraplegia in flexion observed by these authors, however, cogwheel rigidity appears to have been noted mainly in the upper extremities, while signs of pyramidal involvement predominated in the lower limbs.

The belief that centers in the brain stem are capable of keeping the lower extremities in an extended position seems to be based largely on the immediate effects of decerebration. Bazett and Penfield's experience with chronic decerebrate preparations suggests that these centers may fail to exercise their usual function when isolated for a time from higher levels.[76] The occurrence of flexion contracture as a terminal event in physically and mentally deteriorated patients with diffuse cerebral disease is probably not without significance in this respect. It would appear that in the process of dissolution primitive forms of response may get out of hand even when prespinal connections ordinarily capable of restraining them are, anatomically at least, still intact.

SUMMARY

The frequent involuntary movements of the lower limbs characteristic of spastic paraplegia in flexion are identical with the flexor reflex or withdrawal reaction, which is greatly exaggerated in this condition. These movements result from various stimuli to which parts below the level of the lesion are unavoidably exposed. Although the patellar and achilles reflexes, particularly the former, may be sluggish or unobtainable, the hamstring reflexes remain active.

Extramedullary tumor and caries of the spine are perhaps the most frequent causes of paraplegia in flexion. The condition has been seen, however, in a number of cases of intramedullary tumor, multiple sclerosis, acute myelitis, acute encephalomyelitis and subacute combined degeneration. It may be associated with any lesion of the cord which

76. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as in the Acute Condition, Brain **45**:185, 1922

leaves the reflex pathways of the lumbosacral segments functionally intact and isolates these segments to a considerable degree from the influence of higher levels.

Although always the result, in cases of lesions of the cord, of extensive interference with spinal conduction, paraplegia in flexion is not necessarily indicative of an irreversible lesion. Though generally coming on some time after the lower limbs are entirely paralyzed, it may appear relatively early when the paraplegia has an abrupt onset or is rapidly progressive.

When reflexes return to the lower limbs after complete transection of the cord, they behave in a manner more or less characteristic of paraplegia in flexion; if a spastic contracture develops it is generally one in flexion. When the cord is gradually compressed to a degree amounting to total section, however, the extensor muscles may remain in a spastic state over long periods.

Paraplegia in flexion resulting from supraspinal lesions appears to be most frequent in cases of diffuse cerebral degeneration with progressive dementia and pseudobulbar palsy.

Development of a spastic contracture in flexion is due primarily to exaggeration of the flexor reflex. As the lower limbs are brought into the flexed position, a fixation reflex, or shortening reaction, is induced in the flexor muscles. This reflex tends to hold the limbs in a flexed position for longer and longer intervals until the stretch reflex becomes augmented to the degree that the limbs can no longer be passively extended.

There is ample evidence, both clinical and experimental, to support the view that for any great release of flexor reflexes not only the pyramidal tracts but other descending pathways must be involved.

Decubitus ulcers and other sources of painful stimuli are a potent factor in the exaggeration of the flexor reflex. A poor general condition, which is believed to have a depressing effect on the extensor reflexes, may also contribute to the development of a flexion contracture. There is reason to suspect that, on occasion, these two factors have the effect of a more extensive anatomic lesion in the central nervous system.

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AMYOTROPHIC LATERAL SCLEROSIS

ANATOMIC AND PATHOLOGIC CONSIDERATIONS

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Easy as it is to recognize a typical case of amyotrophic lateral sclerosis, the diagnosis of an atypical form of this morbid condition is often difficult. Pathologically evidenced by degeneration of the system of the motor ganglion cells of the cortex, medulla and spinal cord, a typical case of amyotrophic lateral sclerosis manifests itself clinically by a combination of atrophies of the muscles innervated by the bulbar and spinal nerves and spasticity of the extremities, especially the lower. The atrophies are the result of degeneration of the motor cells of the medulla and spinal cord; the spasticity is the result of degeneration of the motor cells of the cortex and the consequent degeneration of the pyramidal tracts.

As has been emphasized on several occasions,[1] the clinical picture of amyotrophic lateral sclerosis may be a manifestation of involvement of only a part of the system of the motor cells. For instance, the motor cells of the medulla may be mainly affected. The clinical picture then will be that of bulbar paralysis, while the other two components (muscular atrophies and spasticity) will be in the background or absent. However, even in cases of bulbar paralysis it is possible to demonstrate changes in the motor cells of the cortex and the spinal cord, especially if paralysis had lasted for a great length of time. On the other hand, the clinical picture may appear as progressive muscular atrophy (spinal type of Aran and Duchenne), indefinitely remain as such, and yet show

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1. Hassin, G. B.: A Case of Amyotrophic Lateral Sclerosis in the Form of a Progressively Developing Triplegia, New York M. J. **106**:932, 1917; Bulbar Paralysis of Amyotrophic Lateral Sclerosis?: A Clinico-Pathologic Note, Arch. Neurol. & Psychiat. **2**:261 (Sept.) 1919; Degenerative Erkrankungen mit besonderer Bevorzugung motorischer Leitungsbahnen und Kerne und kombinierte Systemerkrankungen, Monatschr. f. Psychiat. u. Neurol. **86**:17, 1933; Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933.

histologic changes in the medulla and motor cortex, as they were described by Alzheimer,[2] for instance. Involvement of the third anatomic component (the cortical motor cells), which gives origin to corticospinal pyramidal fibers, should theoretically result in spastic paralysis of the lower, or of both lower and upper, extremities. Such a condition has been described by Charcot [3] and, after him, more systematically by Erb [4] as spastic paraplegia, or lateral sclerosis. Sensory, trophic, genitourinary or vasomotor disturbances are absent in this form of paralysis, which is also known as Charcot-Erb's disease. Pathologic reports of this condition are scanty, and, as they belong for the most part to earlier days, they are not complete, being anatomic rather than histologic. Yet such reports demonstrated that the degeneration of the pyramidal fibers is associated with involvement, though slight, of other tracts of fibers. In general, one may assume that clinically Charcot-Erb's disease is amyotrophic lateral sclerosis minus bulbar paralysis and progressive muscular atrophy; that bulbar paralysis is amyotrophic lateral sclerosis minus spastic paraplegia and progressive muscular atrophy, and that progressive muscular atrophy is amyotrophic lateral sclerosis minus bulbar paralysis and spastic paraplegia.

The clinical picture of degeneration of the pyramidal tract resembles still more what Mills [5] described as progressive ascending and descending hemiplegia (Mills's disease). That is, it is permissible to assume that the destruction of the cortical motor cells resulting in a spastic condition of the extremities is the sole manifestation of amyotrophic lateral sclerosis. It may dominate the clinical picture for a long period, and ultimately become complicated by bulbar paralysis and spinal amyotrophies and result in a typical picture of amyotrophic lateral sclerosis. In Mills's disease weakness sets in first in one leg, whence it extends, months or years later, to the ipsilateral upper extremity, but is always more marked in the leg. In exceptional cases, also, the lower branch of the corresponding facial nerve may become affected. The weakness culminates in paralysis of one half of the body, with the tendon reflexes exaggerated and the sensory, trophic and sphincter disturbances absent. Later the opposite side may become involved.

2. Alzheimer, A.: Ueber einen Fall von spinaler progressiver Muskelatrophie, Arch. f. Psychiat. **23**:459, 1892.

3. Charcot, J.: Gaz. hebd. de méd., 1865, no. 7; cited by Erb.[4b]

4. Erb, W.: (*a*) Ueber einen wenig bekannten spinalen Symptomencomplex, Berl. klin. Wchnschr. **12**:357, 1875; (*b*) Ueber die spastische Spinalparalyse (Tabes dorsal spasmodique, Charcot), Virchows Arch. f. path. Anat. **70**:241, 1877.

5. Mills, C. K.: A Case of Unilateral Progressive Ascending Paralysis Probably Representing a New Form of Degenerative Disease, J. Nerv. & Ment. Dis. **27**:195, 1900; Unilateral Ascending Paralysis and Unilateral Descending Paralysis: Their Clinical Varieties and Their Pathologic Causes, J. A. M. A. **47**:1639 (Nov. 17) 1906.

In a case of "ascending unilateral amyotrophic lateral sclerosis" Spiller [6] observed new and old degeneration of the pyramidal fibers, which he traced to the cortex or the internal capsule, and, what is even more noteworthy, he also found changes in the cells of the anterior horns of the spinal cord. Mills himself conceded that in the syndrome described by him the cells of the ventral horns may eventually become degenerated and thus produce a picture of amyotrophic lateral sclerosis, provided the patient lives long enough. Though clinical and pathologic studies are scarce, it is permissible to assume that in both Mills's disease and the Charcot-Erb syndrome the clinical features are essentially the same and pertain mainly to degeneration of the pyramidal fibers, and that both in all probability are manifestations of amyotrophic lateral sclerosis.

The components of amyotrophic lateral sclerosis (bulbar paralysis, progressive muscular atrophy, Mills's disease) are generally considered as separate pathologic entities and therefore are easy to recognize. In some instances the components form atypical combinations and therefore render the diagnosis uncertain. Three such cases have come under my observation; 1 has been studied pathologically.

REPORT OF CASES

CASE 1.—*Bulbar paralysis and flaccid paraplegia of the lower extremities with muscular atrophies and loss of the tendon reflexes; widespread degeneration of the anterior horns of the spinal cord, motor nuclei of the medulla and the pyramidal nerve fibers.*

History.—A white woman aged 60 was seen by me on June 18, 1938, in consultation with Drs. Ludwig Loeb and Regina Stolz Greenebaum, because of paralysis of the lower extremities and anomalous bulbar manifestations, both of two years' duration. The patient had been in good health until about two and one-half years previously, when she commenced to experience progressive weakness in the knees and legs and "general nervousness." The symptoms became complicated later with disturbances of speech, which became unintelligible. There were no pain or urinary disturbances. About five months after the onset of the weakness and the "general nervousness," thyroidectomy was performed, without favorable results. The patient grew steadily worse; she was unable to walk, speak, swallow or chew and became emaciated.

Examination.—The patient was a tall, lean woman, who lay in bed on her back. There were scars from thyroidectomy and appendectomy. The entire musculature—of the face, body and all the extremities—was wasted. The mental condition was clear, but there were attacks of involuntary, uncontrollable crying. The lower extremities were paralyzed and the feet were drooping, but the upper extremities moved freely. Though questions were comprehended, the answers were not understood because of complete anarthria. There was no drooling of saliva. The pupils reacted well to light and in accommodation; the nerves and muscles of the eyes and the fundi were normal. All the muscles of the face supplied by the fifth and seventh nerves were thin and atrophied, so that the

6. Spiller, W.: Primary Degeneration of the Pyramidal Tracts: A Study of Eight Cases with Necropsy, Univ. Pennsylvania M. Bull. **17**:390, 1904-1905.

patient was unable to whistle, chew, pucker her lips or bring them together or close her eyes firmly. The tongue could not be protruded beyond the teeth and was thin, furrowed and fibrillating. The pharynx was engorged.

The lower extremities were "mainly bones;" the skin was edematous, both feet were drooping, slightly inverted and (especially the right) could not be flexed, extended or everted. The flexion and extension power of the knees was weak on the right side; in the hips the power of flexion, adduction and external rotation was fair. Though the upper extremities were not paralyzed, they were weak and wasted; a claw position of the hands was not in evidence.

Reflexes: The pupillary reflex was normal, both to light and in accommodation; the mandibular reflex was exaggerated; the biceps and triceps reflexes were diminished; the knee and ankle jerks were absent on the right and present on the left; the abdominal reflex and the Babinski sign were not elicited.

Sensibility: Sensation for all modalities was normal throughout.

Course.—The patient became steadily worse: the paralysis of the lower extremities became completely flaccid; both patellar and ankle reflexes disappeared; power in the upper extremities became diminished and the reflexes in them were obtained with difficulty; the bulbar disturbances persisted. Nine months after my examination, and about three years after the onset of the disease, the patient died.

Comment on the Clinical Phenomena.—The clinical picture was that of incomplete amyotrophic lateral sclerosis, in which the spastic element was missing and only the other two components—progressive muscular atrophy and bulbar paralysis—were present. The only sign of involvement of the pyramidal system of fibers was an exaggerated mandibular reflex. The other signs (rigidity of the extremities and exaggerated tendon reflexes) were evidently overshadowed by the extensive destruction of the motor cells of the spinal cord and medulla. The process probably commenced simultaneously in both the medulla and the spinal cord, and clinically resulted in an incomplete picture of amyotrophic lateral sclerosis.

Pathologic Observations.—Grossly, the pons, medulla and spinal cord were striking for their smallness; like the brain, they exhibited no other gross anomalies.

Microscopically, the spinal cord revealed combined degeneration of the ventral horns of the spinal cord and of the pyramidal nerve fibers (fig. 1), and other changes in them as described in typical cases of amyotrophic lateral sclerosis.[7] The myelinated nerve fibers and the ganglion cells of the ventral horns of the spinal cord were reduced in size and number and were replaced by glial tissue, capillaries and blood vessels. The changes were present not only in the cervical region of the spinal cord but also in the dorsal, lumbar and sacral areas, and were marked even in the conus medullaris. The few remaining ganglion cells also were reduced in size. Yet, small as they were, they stained well and often retained their Nissl bodies, especially at the periphery; that is, they showed no chromatolysis and only occasionally exhibited neuronophagia. Because of the scarcity of ganglion

7. Hassin, G. B.: Histopathologic Changes in a Case of Amyotrophic Lateral Sclerosis, M. Rec. **91**:22, 1917; Amyotrophic Lateral Sclerosis Complicated by Subacute Combined Degeneration of the Cord: Clinical and Pathologic Report of a Case, Arch. Neurol. & Psychiat. **29**:125 (Jan.) 1933.

cells and myelinated nerve fibers, the anterior horns appeared colorless in sections stained by the modified Weigert-Pal method (fig. 1*A*).

Of great interest in this case were the changes in the ganglion cells in the lumbosacral region of the cord. While in a normal spinal cord or, to a certain extent, in a cord from a classic case of amyotrophic lateral sclerosis the ventral horns are rich in ganglion cells and myelinated nerve fibers, in the present case

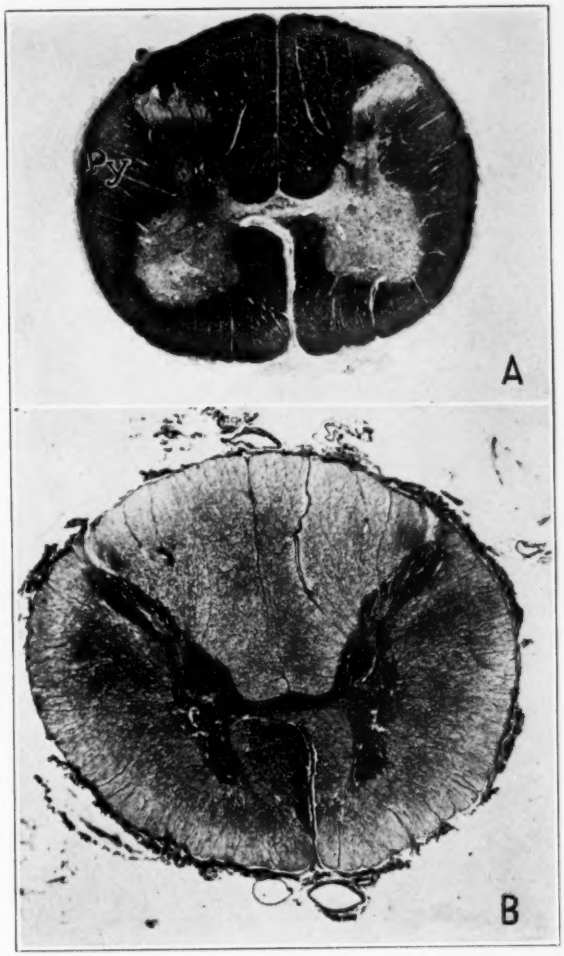


Fig. 1.—*A*, the third lumbar segment of the spinal cord. The ventral horns, especially the right, are devoid of nerve fibers, and therefore appear colorless. The lateral pyramidal tracts (*Py.*) are degenerated. Weil's stain.

B, the eleventh thoracic segment. The dark areas in the anterior and lateral columns are the pyramidal tracts. As is usually the case in amyotrophic lateral sclerosis, the degenerated (dark) areas in the anterior and lateral columns cover larger areas than the spaces assigned to the fibers of the pyramidal tract. Alzheimer-Mann stain.

these areas showed a scarcity of both (fig. 2). In the second lumbar segment, for instance, there were only 4 ganglion cells in the mesial group and 8 in the posterolateral group, instead of 30, and in the first sacral segment the anterolateral group contained 5 ganglion cells instead of 30. Especially impressive are such changes when one contrasts the scarcity of the ganglion cells pictured in figure 2 with their wealth in figure 3, which is taken from a normal spinal cord. It must

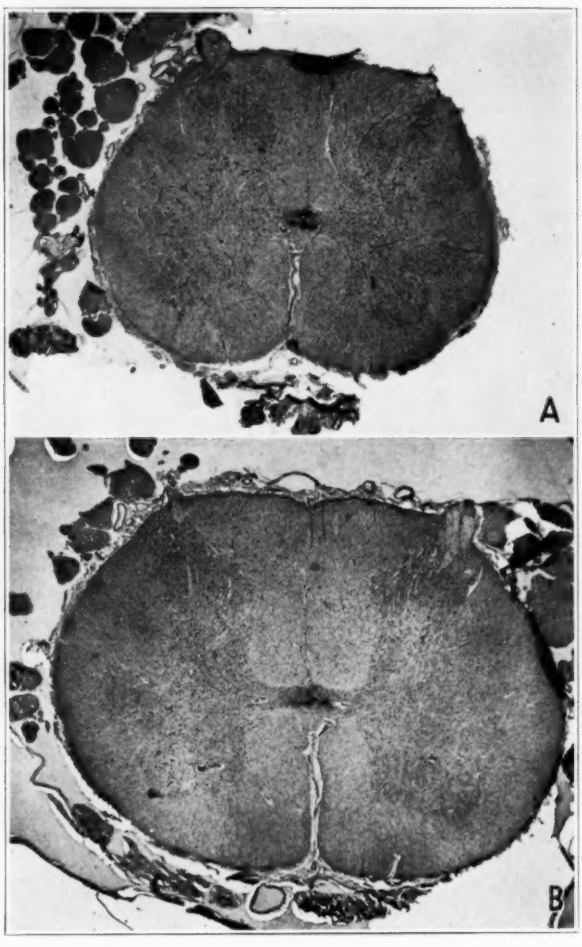


Fig. 2.—*A*, the second sacral segment; *B*, the third lumbar segment. The ventral horns of both segments are poor in ganglion cells. The photographs should be compared with that in figure 3. Toluidine blue stain.

be emphasized again that the cells of the lumbosacral area which escaped destruction were not entirely normal, for they differed from normal ganglion cells in size, shape and scarcity of dendrites.

The destroyed parenchyma of the ventral horns was associated with atrophy of the ventral roots and was replaced by cytoplasmic astrocytes, glia fibers and proliferated oligodendrocytes and microgliocytes. The astrocytes and microglio-

cytes, which are absent in a normal spinal cord, were conspicuous in this case throughout the spinal segments, not excepting the conus medullaris.

Changes in the ganglion cells similar to those of the spinal cord were also marked in the nuclei of the motor nerves of the medulla and pons, and to a certain extent in the ganglion cells of the motor cortex. Thus, the nuclei of the twelfth nerve, the nucleus ambiguous and the nuclei of the fifth and seventh nerves were profoundly degenerated, and for this reason it was often difficult to locate them. The ganglion cells of the cortex were much less affected. The Betz cells, for instance, retained their Nissl bodies; the dendrites were well preserved and neuronophagia was not in evidence; the cells were merely reduced in size. It is noteworthy

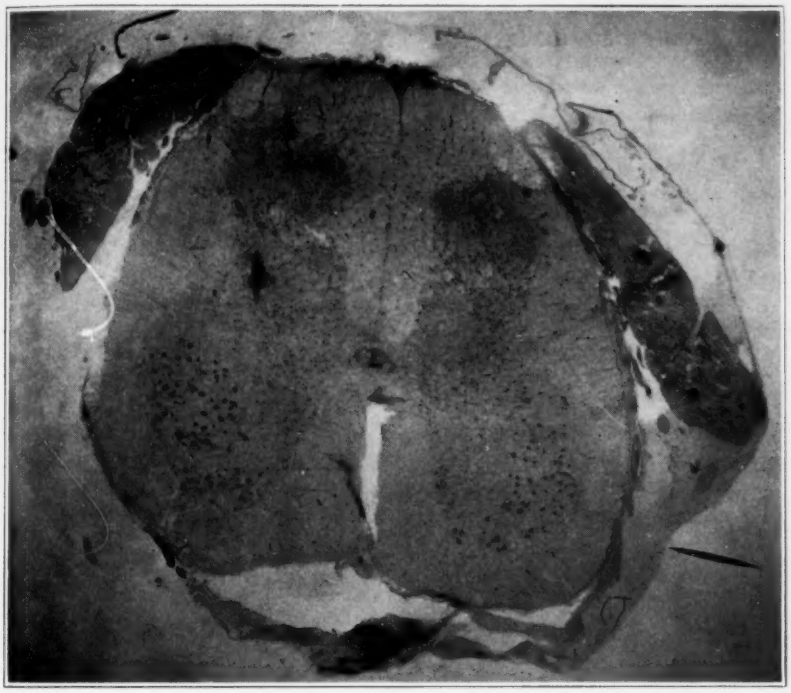


Fig. 3.—The fifth lumbar segment. The anterior horns show a wealth of ganglion cells. The photograph should be compared with those in figure 2. Toluidine blue stain.

that some changes in the ganglion cells also were noticeable in the premotor area, but none were present in the temporal and occipital lobes or elsewhere in the brain stem and the cerebellum. It is also interesting to note that the massive degeneration of the pyramidal tracts, which was so outstanding in the spinal cord, medulla and pons, was not in evidence in the cerebral peduncles and the internal capsule in specimens stained by the Weigert-Pal method. Only with the Alzheimer-Mann method was it possible to detect in the internal capsule, and less easily in the peduncles, abnormal, broken-up nerve fibers. These areas contained numerous Marchi globules, which resulted from the fragmentation of the myelin and which were mixed with myelophages, microgliocytes and an increased number of oligodendrocytes, many of which were supplied with cytoplasm. Basophilic

metachromatic substances and mast cells were present near the capillaries and blood vessels, and lipoids in fat granule bodies were occasionally seen in the adventitial vascular spaces. In short, the pyramidal fibers in the spinal cord were in an advanced stage of degeneration; those of the internal capsule and peduncles were in early stages. The differences in the extent of degeneration of the pyramidal fibers in the spinal cord and in the brain have attracted the attention of investigators and have been given various explanations, which cannot be discussed here.

Mesodermal Tissues—Blood Vessels, Meninges and Choroid Plexus: The blood vessels exhibited no infiltrations of the adventitial spaces with hematogenous elements—lymphocytes and plasma cells—but their thickened walls often contained macrophages which were packed with granules of dark blue pigment and fat granule bodies and, as has been mentioned, were occasionally surrounded by mast cells. As in other degenerative states, the hyperplasia and thickening of the vessel walls were here secondary to the presence in them of fat granule corpuscles, which acted like foreign bodies and provoked a mesodermal reaction. Though the thickening of the walls of the capillaries and blood vessels was sometimes extensive, it did not affect the size of the lumens, which always remained patent. In some instances the blood vessels of the septums of the spinal cord were slightly infiltrated with lymphocytes and resembled a similar condition in the pia. Like the blood vessels, both the central and the spinal pia-arachnoid were thickened and contained fat granule bodies, which were occasionally mixed with lymphocytes.

The choroid plexus consisted of a normal stroma, hyperemic blood vessels and unusually large, honeycombed tuft cells, which appeared filled with minute lipoid granules in specimens stained with scarlet red and sudan III.

The noteworthy feature in this case was flaccid lower paraplegia in the presence of degeneration of the pyramidal tracts, instead of spasticity and exaggerated reflexes, which are typical of amyotrophic lateral sclerosis. One must therefore concede that flaccid paraplegia is not incompatible with degeneration of the pyramidal tracts, at least in some cases of amyotrophic lateral sclerosis. Another interesting feature was the condition of the pons. The nests of ganglion cells in the pons and the fibers emanating from them to form the brachia pontis (middle cerebellar peduncles) were here unaffected (fig. 4), while the bundles of the pyramidal fibers occupying the central portion of the pons appeared degenerated. The picture is the reverse of that seen in cases of olivopontocerebellar atrophy, in which the central portion carrying the pyramidal fibers is preserved and the brachia pontis are affected (fig. 5). The degeneration of the brachia pontis is due to destruction of the nests of the pontile ganglion cells, which, as has been emphasized elsewhere,[8] together with the ganglion cells of the bulbar olives and of the arcuate nuclei, form the so-called cell bands of Essick. The cell bands belong to one system, possess a common ancestry (the rhomboid lip) and succumb together, giving rise to a clinical syndrome known as olivopontocerebellar atrophy (incoordination and disturbances of gait

8. Hassin, G. B., and Harris, T.: Olivopontocerebellar Atrophy, Arch. Neurol. & Psychiat. **35**:43 (Jan.) 1936; Marie's Ataxia (Olivopontocerebellar Atrophy) ibid. **37**:1371 (June) 1937.

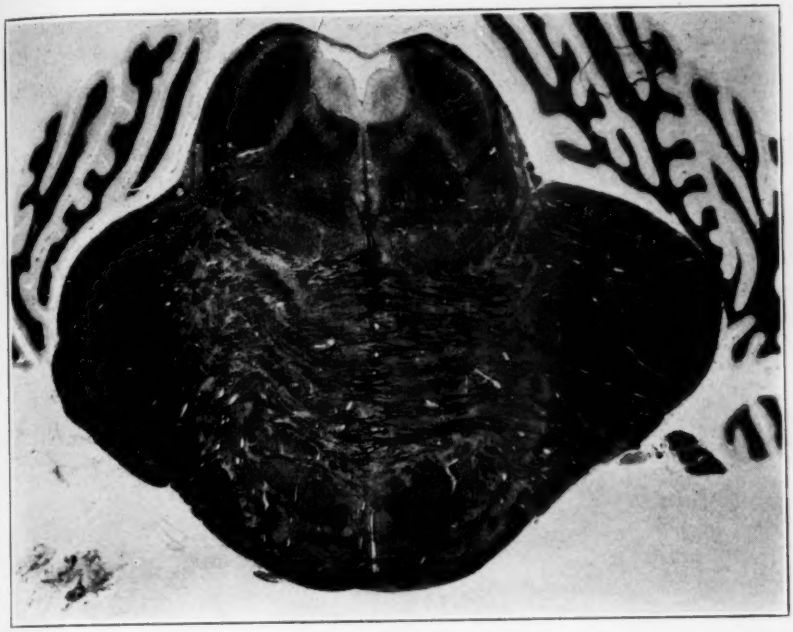


Fig. 4.—The central portion of the pons contains degenerated pyramidal fibers; the lateral, densely stained areas are the middle cerebral peduncles. The photographs should be compared with that in figure 5. Weil's stain.

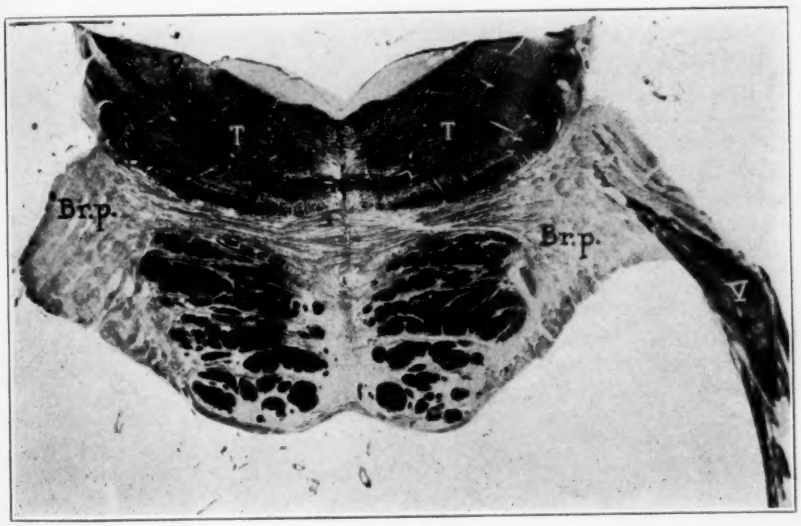


Fig. 5.—The bundles in the pons are normal pyramidal tracts; the lateral parts (*Br. p.*) are the middle cerebral peduncles. The superior cerebral peduncles are indicated by *s. p.* Pal-Kultschitzky stain.

and speech). Like amyotrophic lateral sclerosis, olivopontocerebellar atrophy may be incomplete. It may occur as olivocerebellar atrophy, for instance, but the two conditions are never combined. Thus, the motor cells do not become atrophied in olivopontocerebellar atrophy, and the cell bands of Essick are not affected in amyotrophic lateral sclerosis. However, both give rise to secondary nerve degeneration—of the motor fibers in one and of the cerebellar fibers in the other—producing in olivopontocerebellar atrophy typical clinical features: ataxia and difficulties of speech and gait. The exact cause of the cell atrophies is not known in either condition. It is probably an inborn defect, either abiotrophy in the sense of Gowers or what Vogt [9] termed *Pathoklise*. Pathoklisis was defined by C. and O. Vogt as abnormal vulnerability of certain systems of ganglion cells or nerve fibers which may become an active disease process in certain stages of life. Whether the anomaly is prompted by physicochemical or by other factors is not possible to tell, but the fact is that at present two morbid conditions may be discerned in which certain groups of ganglion cells, by becoming deficient, cause definite but varied motor disorders. In one condition it is exquisitely motor; in the other it is in the form of incoordination.

In the following 2 cases only some elements of amyotrophic lateral sclerosis were in evidence, and for this reason they were hard to classify. Pathologically, however, the cases in all probability represent amyotrophic lateral sclerosis.

CASE 2.—*Flaccid paralysis with drooping of both feet; atrophy of and fibrillary twitchings especially in the muscles of the lower extremities; loss of the knee and ankle jerks; exaggerated biceps, triceps and periosteal reflexes.*

History.—A white woman aged 52 was admitted to the Research and Educational Hospitals on Nov. 25, 1938, because of paralysis of the lower extremities. One year previously she commenced to experience "stiffness" in both legs. The "stiffness developed gradually," while the weakness was so great that the patient could not lift herself out of a chair without the use of her hands. At the same time twitchings appeared in the muscles of the right thigh; the right ankle would "turn," and the gait became unsteady. About six months after the onset the lower portion of the right leg became weak; the foot was drooping and had to be held up in bed with pillows. From the right leg the weakness extended to the left and involved the extensor muscles first of the right and later of the left foot. The twitchings and weakness gradually increased in the leg, thighs and upper extremities, so that ten months after the onset of the weakness the patient could not extend the left leg.

There were dull aching in the knees, elbows and shoulders and an occasional feeling of crawling in the thighs. Otherwise, there were no sensory, urinary or gastrointestinal complaints.

Examination.—There were marked fibrillary twitchings in both upper and lower extremities; paralysis of both lower extremities, which were flexed and flabby;

9. Vogt, O.: Der Begriff der Pathoklise, J. f. Psychol. u. Neurol. **31**:245, 1924-1925.

drooping and cyanosis of both feet; no paralysis of or atrophy in the muscles of the upper extremities or those supplied by the cranial nerves; loss of the knee and ankle jerks; exaggeration of the biceps, triceps and periosteal reflexes, including the mandibular; a Hoffmann sign bilaterally, and loss of the abdominal reflexes. Sensibility was normal. Examination of the gastric juice, spinal fluid and genitourinary organs gave normal findings.

This case differs from the previous one in the absence of bulbar paralysis, but resembles it in the presence of lower flaccid paraplegia, atrophies, loss of reflexes in the lower extremities and their presence in the upper extremities and the lower jaw and in the absence of sensory and genitourinary disturbances. The left leg was kept flexed because the patient experienced severe pain in the limb on attempts to extend it. The pain was probably of arthritic origin. The vivid fibrillary twitchings and the exaggerated mandibular and tendon reflexes of the upper extremities suggested amyotrophic lateral sclerosis, which thus in this case was represented only by atrophies and signs of involvement of the pyramidal tract (fibers for the upper extremities and the lower jaw). In the gradual development of the paralysis, first in one leg and later in the other, the condition in this case resembles Mills's disease, but the spastic phenomena in the lower extremities were lacking. Neither is the case clinically a typical instance of amyotrophic lateral sclerosis, though, as in the previous case, it may prove to be such pathologically.

CASE 3.—*Fibrillary twitchings; muscular weakness in the lower extremities, and signs of involvement of the pyramidal tracts.*

History.—A Negro aged 46 was transferred to the neurologic service of Cook County Hospital on Dec. 5, 1938 from a medical ward, in which a diagnosis of cervical rib was made.

Except for a fracture of the left humerus, of fifteen years' standing, the patient had been in good health. One year prior to his entrance to the hospital the patient commenced to experience dull pain in the neck, shoulders and lumbar region, with numbness in the hands; in addition, there was a feeling of weakness in the hands and legs.

Examination.—There were an extensive scar over the left humerus, with atrophy of the left forearm and ipsilateral wrist drop; decreased muscle power in all the extremities, with somewhat impaired motility in the shoulder joints, elbow and wrists; exaggerated tendon and periosteal reflexes, including the scapular and mandibular (4 plus); absence of the Babinski sign; marked fibrillary twitchings and some atrophy of both serratus muscles, but none in the small muscles of the hands; normal coordination, speech and mentality; slightly impaired sensibility for touch over the distribution of the radial nerve in the left hand (old fracture of the left forearm), and a shuffling, "slow" gait. The genitourinary organs were normal. The spinal fluid was normal; there was no evidence of a block, and the serologic reactions were negative.

In this case, aside from the atrophy of the muscles of the forearm, the main clinical features were those of involvement of the pyramidal

tract, as evidenced by weakness in the hands and especially the feet, spastic gait and exaggerated tendon reflexes. The pains which the patient had before he came to the hospital have not been complained of since; they were so indefinite and widespread that they probably formed an independent condition, which had nothing to do with the fundamental clinical picture. This was considered to be that of amyotrophic lateral sclerosis minus bulbar phenomena and atrophies, a condition which, as has been noted, is classified by some as Charcot-Erb's disease, or lateral sclerosis. Charcot, Erb and Strümpell [10] stated that the anatomic cause of this disease is primary degeneration of the pyramidal tract, of its nucleodistal parts (Strümpell). According to Strümpell, the degeneration begins in the lumbar region, extends to the thoracic and cervical portions of the spinal cord and disappears in its upper segments. Occasionally, degeneration of the columns of Goll and Flechsig occurs. Though Strümpell called Charcot-Erb's spastic paraplegia a typical morbid entity, he himself reported a case of spastic paraplegia of long standing in which a picture of amyotrophic lateral sclerosis was ultimately exhibited.

The diagnosis of spastic paraplegia or lateral sclerosis is rarely made by modern neurologists. Raymond [11] and Leyden and Goldscheider [12] questioned the existence of such a specific morbid entity. Yet, as such, it is mentioned even in good textbooks. Resembling Mills's disease (ascending or descending hemiplegia) in the presence of degeneration of the pyramidal tracts, so-called lateral sclerosis differs from it in that paraplegia is the essential manifestation, while in Mills's disease hemiplegia is the essential feature, both forms being probably caused by degenerative lesions of the cortical motor cells. That is, both forms are in all probability incomplete forms of amyotrophic lateral sclerosis, minus bulbar paralysis and amyotrophies.

Unfortunately, there are no histopathologic studies of such atypical forms with modern methods of histopathologic research.

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10. Strümpell, A.: Die primäre Seitenstrangsklerosen (spastische Spinalparalyse), Deutsche Ztschr. f. Nervenh. **27**:291, 1904; Ueber einen Fall von primärer systematischer Degeneration der Pyramidenbahnen, ibid. **5**:225, 1894; Ueber eine bestimmte Form der primären combinierten Systemerkankung des Rückenmarks, Arch. f. Psychiat. **17**:227, 1886.

11. Raymond, in discussion on Babinski, J.: Sur une forme de paraplégie spasmodique consécutive à une lésion organique et sans dégénération du système pyramidal, Bull. et mém. Soc. méd. d. hôp. de Paris **16**:342, 1899.

12. Leyden, E., and Goldscheider, A., in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1905, vol. 10, p. 305.

CONCLUSIONS

1. The clinical picture of amyotrophic lateral sclerosis may be incomplete, and 3 such cases are here recorded.

2. In 1 case the clinical picture somewhat resembled Mills's disease; in another it possessed features of Charcot-Erb's disease (so-called spastic paraplegia).

3. Flaccid paraplegia with loss of tendon reflexes may occur in the presence of degenerated pyramidal tracts.

4. In amyotrophic lateral sclerosis the pathologic picture of the pons is the reverse of that in olivopontocerebellar atrophy, in which a different system of ganglion cells is affected.

Case Reports

MENINGIOMA SHOWING SARCOMATOUS DEGENERATION

F. Keith Bradford, M.D., Houston, Texas, and
A. J. Miller, M.D., Louisville, Ky.

Meningeal tumors showing both benign and malignant portions are relatively uncommon. However, the case to be presented is more unusual in that it is an example of a malignant tumor apparently arising from the margin of a benign meningioma, the two growths being contiguous but not blended. In addition, this tumor had an uncommon site, since it was limited to the inferior surface of the cerebellum without involving any major dural sinuses. Localization was made possible through involvement of bone by the benign portion of the tumor before clinical findings were more than suggestive.

REPORT OF CASE

Irritability for four months, feeling of unsteadiness for three months and vague discomfort in the back of neck for one month. Unsustained horizontal nystagmus on looking to the right, slight unsteadiness for a few steps after rising suddenly and moderate suboccipital tenderness on the right side. Erosion of both tables of the skull in the right suboccipital area. Removal of a meningioma involving dura and bone. Complete recovery for one and a half years, until time of writing, without roentgen irradiation.

History.—J. C., a business man aged 51, was in perfect health until August 1937, when he became more irritable with his family and business associates than was his custom. While on a vacation in the mountains in September 1937, the patient was first aware of a feeling of insecurity in high places. He had a feeling of unsteadiness or dizziness which he found difficult to describe. There was no change in his gait or station apparent to those who knew him. He returned to work and continued without any particular symptoms until October 1937, when he noticed a constant feeling of uncertainty in walking. Although the patient frequently used the word "dizzy" in describing the feeling, further questioning made it apparent that it was not true vertigo. He found the greatest difficulty in walking immediately after he arose from a chair. During November he stopped work and spent most of his time in bed because of the uncomfortable uncertainty he experienced while up and about. Only with leading questions was it possible to ascertain that he occasionally felt a vague discomfort—never a headache—in the back of his head and neck. Once in November the patient thought he saw double for several hours, but was not positive about it.

From the Departments of Surgery and Pathology, the University of Louisville School of Medicine.

Vision in the left eye had been poor since boyhood. The patient attributed loss of vision to injury by a small piece of steel. The past personal and family histories were without significance. There was no history of von Recklinghausen's disease.

Physical Examination.—General physical examination gave normal results.

Neurologic Examination.—The cranial nerves were normal except for the following finds: There were a few horizontal nystagmic jerks on looking to the right; the optic disks were of good color, with crisp outlines and no engorgement of the veins; a circumscribed area of choroiditis was present in the left macular area; the right visual field was normal, and the left showed a complete central scotoma



Fig. 1.—An area of decreased density, 2 cm. in diameter, is seen below the groove for the lateral sinus, to the right of the midline. This was found by stereoscopic studies to represent erosion of both tables of the skull. Above and below are smaller areas of involvement.

with a normal peripheral field. The mental state was entirely normal. Tests for motor function did not show weakness, dysdiadokokinesis, hypotonia, dysmetria or past pointing. The patient could walk tandem satisfactorily. If he stood up suddenly after being seated in a chair the first few steps were slightly awkward, but the subjective feeling of unsteadiness was disproportionate. Bending the trunk to a right angle with the lower extremities and straightening suddenly or walking with the neck hyperextended produced again subjective unsteadiness, with but little objective evidence of ataxia. Definite but not marked suboccipital tenderness was present, which was greater on the right side. The tendon, superficial and plantar reflexes were normal.

Roentgenologic Examination.—The skull (fig. 1) showed a round area of decreased density, 2 cm. in diameter, below the right lateral sinus and to the right of the midline, which apparently involved both tables of the skull. Similar but smaller defects were present to the right of the midline just above the foramen magnum. Roentgenologic examination of the chest revealed nothing abnormal.

Clinical Course.—With a possible atypical Ménière's syndrome in mind, a sodium-free diet and ammonium chloride, 3 Gm. daily for ten days, were given, without improvement. It was then decided that suboccipital exploration was justified by the roentgenologic findings, despite the relatively indeterminate symptoms.

Operation.—On Dec. 1, 1937, Dr. R. G. Spurling made a mastoid to mastoid incision and separated the galea from the deep fascia. The suboccipital muscles were divided near their insertion and retracted to expose the suboccipital area down to the foramen magnum. There was brisk bleeding from an area, 2.5 cm. in diameter, below the lateral sinus and to the right of the midline, where the tumor protruded through a defect in the skull and invaded the muscle. This was readily controlled with the cautery and cottonoid strips. Two smaller defects in the occipital bone appeared between the large defect and the foramen magnum. More bone was removed, normal dura being exposed around the tumor and the defect extended above to within 1 cm. of the lateral sinus and torcula, below to within a narrow rim of the foramen magnum and to the left just beyond the occipital sinus. It was then possible to apply silver clips about the margin of the normal dura and free completely the tumor from its dural attachment without encroaching on either the lateral or the occipital sinus. On lifting the portion of the tumor invading the dura, it was evident that a papillomatous projection of the tumor extended to a depth of about 5 cm. into the cerebellum, just to the right of the vermis. However, there was no additional attachment of the tumor, which was lifted out of the hole it had made in the cerebellum without bleeding. Where the tumor had invaded the suboccipital muscle it was cleanly excised. The wound was thoroughly dried and the usual closure made. The patient's condition remained uniformly good throughout the procedure.

Postoperative Course.—The patient made an excellent postoperative recovery. A small superficial area of pressure necrosis in the skin incision delayed healing for several days. The patient was discharged from the hospital on the eighteenth postoperative day. His feeling of unsteadiness gradually left him during the first month and after a vacation he returned to active work, eight weeks after the operation. He has continued to be free from symptoms. Roentgen therapy was not administered at any time. At the last observation (May 29, 1939) there were no complaints. The patient mentioned slight paresthesias above the surgical incision, where sensation had returned. He had noticed increase in presbyopia during the past two years. Irregularity in gait was not noted. Neurologic examination revealed normal optic disks. The central area of choroiditis and central scotoma in the left eye were unchanged. Nystagmus was not present. There was no dysdiadokokinesis or dysmetria. Station was normal with the eyes open or closed. The patient walked tandem easily and could hop readily on either foot. The reflexes were normal.

Pathologic Observations.—Grossly, the tumor was hourglass in shape (fig. 2 *A*) and weighed approximately 64 Gm. One mass was rounded, with a smooth surface except for a rough area where the tumor had been cut away from the surrounding dura mater, leaving a margin of dura attached to the base of the tumor. At its extremity, opposite the area of dural attachment, the rounded mass narrowed into a pedicle about one third the diameter of the tumor and then enlarged into another

mass. After fixation the mass attached to the dura mater measured approximately 4 by 2.5 cm., and the other mass, approximately 3.5 by 4 cm. The latter mass had a well formed capsule and was lobulated. The sectioned surface (fig. 2 *B*) showed the difference in structure. The portion attached to the dura mater was uniformly grayish, somewhat resembling lymph node tissue, and was friable. The nodular mass was strandlike and firm and was not friable. The pedicle between the two tended to separate, but there appeared to be true continuity of tissue.

Sections of the two portions were of different histologic structure. The round mass with the dural attachment was made up of elongated cells arranged in bundles and whorls (fig. 3 *A*). They had a moderate amount of cytoplasm. Palisading was not observed. A small amount of stroma could be made out. The blood vessels were fairly well formed. The shape and arrangement of the cells were suggestive of neurofibroma, but some of the characteristics of this tumor were lacking. There was no fibrosis. Only one or two mitotic figures were found in this portion of the tumor after prolonged search. Silver impregnation revealed a

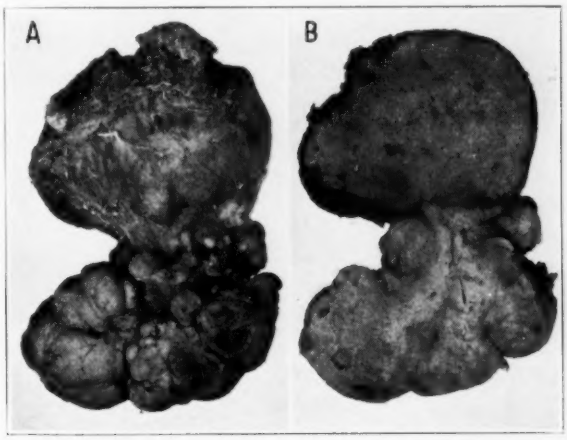


Fig. 2.—*A*, photograph of the tumor, about nine tenths of the natural size. The rounded mass above was attached to the dura mater at its upper extremity. The nodular mass below had no attachment other than the narrow pedicle joining it to the upper mass.

B, section of the tumor revealing the sharp transition in structure between the two masses at the pedicle joining them.

rich reticulum of the same pattern, which grouped the cells into bundles and whorls (fig. 3 *B*).

Sections of the lobulated tumor (fig. 3 *C*), which was attached by a narrow pedicle to the tumor just described, revealed great cellularity with no arrangement into tissue structure. The cells were round and had a small amount of faintly stained cytoplasm without processes. Mitoses were abundant, although there was uniformity of cell form. Silver stains (fig. 3 *D*) revealed a very small amount of reticulum, evenly distributed except near the blood vessels. No glial substance was found with phosphotungstic acid hematoxylin stains. There was no calcification.

Sections through the stalk revealed a line of cleavage in which there was fibrous connective tissue, except for a very narrow area where the two types of cells

intermingled. It seems probable that the lobulated tumor occurred as a result of malignant change in the periphery of the benign tumor, which was attached to the dura.

Interpretation.—The diagnosis was meningioma with malignant change.

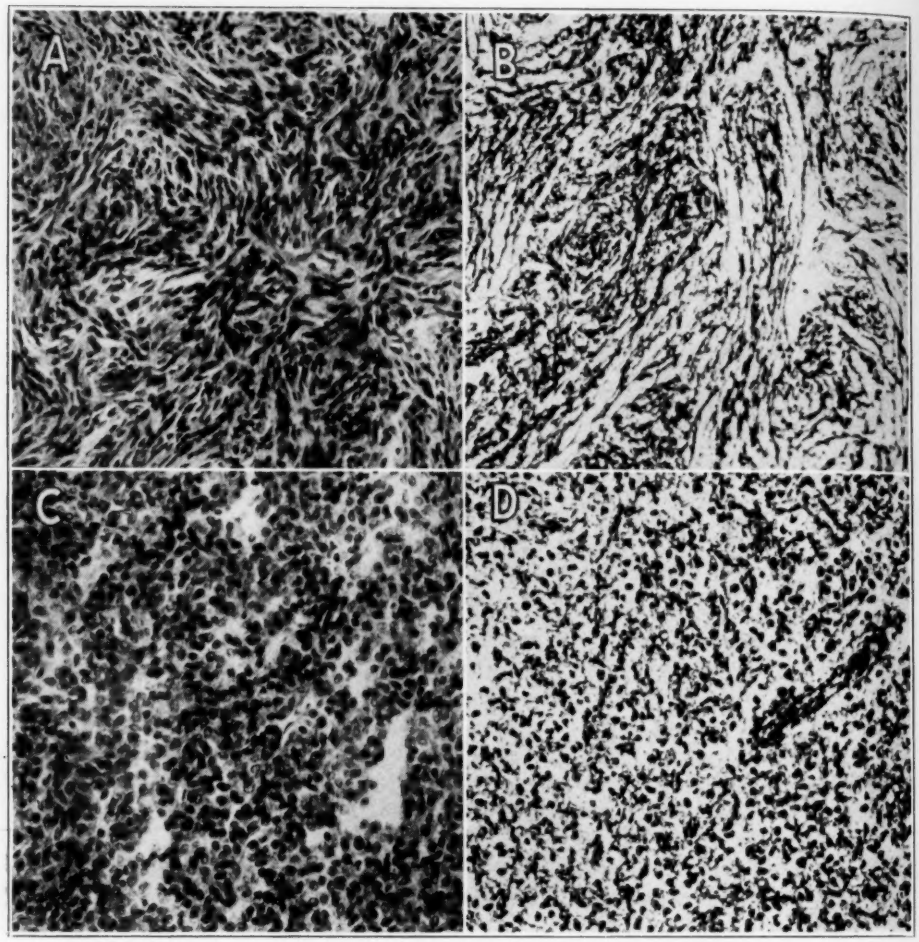


Fig. 3.—*A,* section of the benign portion of the tumor attached to the dura mater (hematoxylin and eosin stain; × 140). The cells are arranged in interlacing strands and whorls. They are elongated and have a moderate amount of cytoplasm.

B, silver impregnation of the benign portion, revealing abundant coarse reticulum, which is arranged in the same pattern as the bundles and whorls of cells.

C, section of the deeper nodular mass (hematoxylin and eosin stain; × 140). The tumor cells are round, with many mitoses, some of which can be identified with this magnification. There are numerous tissue spaces, with no arrangement into tissue structures.

D, silver impregnation of the malignant portion, revealing a sparse reticulum, evenly distributed except near the small blood vessels. There is no tissue organization.

COMMENT

The case presented represents a single intracranial neoplasm composed of two parts with widely different histologic pictures. It seems reasonable to assume that the benign part of the neoplasm, which had invaded the dura mater and bone, was the older portion of the tumor and that in the margin of this older neoplasm a malignant change took place, so that the malignant tumor sprang from the benign one. It had no attachment other than the benign tumor. The location of the tumor and the involvement of the dura mater by it correspond closely to the picture in serial case no. 225 in Cushing's monograph.[1]

In his monograph Cushing described type 6 meningioma as a "fibroblastic meningioma of malignant type," which represents the most unfavorable forms. The longest survival in cases of this type was two and a half years, even after apparent complete extirpation. Tumors of this type tended to recur in a few months. Cushing subdivided the type 6 group into variant 1, containing fusiform cells, and variant 2, containing round cells. Both contain many mitotic figures.

The malignant portion of the tumor here reported corresponds, then, with type 6, variant 2, and apparently arose from a benign meningioma which Cushing would probably have classified as type 3, variant 2.

Probably the short history of four months was due to the fact that after the sarcomatous change occurred growth proceeded in the newly formed part of the tumor at a much greater rate than before.

SUMMARY AND CONCLUSIONS

In this case there was a period of only four months between the first symptom and the operation, and in this short time the patient had become incapacitated, although there were no signs or symptoms of intracranial pressure. The rather intangible cerebellar symptoms and signs were easily confused with true vertigo. The operation, therefore, was performed almost purely on the basis of the roentgenologic findings.

At operation there was complete morphologic extirpation of the neoplasm, including the marginal dura mater. The dura mater and the bone and muscle involved formed the total attachment of the tumor. Roentgen therapy was not given in this case in order not to confuse the result.

Pathologically, the neoplasm was composed of two types, differing in architecture, cellularity, stroma and cell growth. The tumor seems to be a true example of a highly malignant sarcomatous tumor developing in the margin of a benign meningioma. The recovery of the patient for a period of a year and a half without roentgen therapy may indicate a cure, which is unusual in cases of tumors of this histologic type.

NOTE.—The patient had continued in perfect health when heard from Nov. 16, 1939, almost two years after operation.

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1. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End Results, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

EFFECT OF INSULIN SHOCK ON THE HEART AND BLOOD PRESSURE IN TREATMENT OF SCHIZOPHRENIA

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Insulin shock treatment has become a widely used method of combating schizophrenia. As many favorable results of this therapy have been reported, it was decided to follow the effect of the treatment on the size of the heart by measurement of the cardiac shadow in routine roentgenograms taken at a distance of 7 feet (213.4 cm.) at intervals during the course and after cessation of the treatment. Whenever possible, daily determinations of blood pressure were also made. It is our purpose in this paper to present a summary of our findings, giving attention particularly to changes in the size of the cardiac shadow and, second, to changes in blood pressure.

Six regularly committed schizophrenic patients at the Metropolitan State Hospital were selected for insulin shock therapy. All the patients showed the cardinal symptoms of dementia praecox: hallucinations; loosely knit, unsystematized delusions; incoherence; irrelevancy; blocking; mannerisms; seclusiveness; intrapsychic ataxia; lack of insight; poor judgment, and varying degrees of emotional and intellectual deterioration. In all cases the diagnosis of schizophrenia had been unanimously made by the hospital staff. Careful physical and laboratory examinations ruled out the presence of physical disease. Three patients were in the paranoid group, and 3 were in the hebephrenic group. Physically, most of the patients had cold, clammy, cyanotic extremities, pale cheeks and lips and low blood pressure.

Roentgenograms of the heart taken at a distance of 7 feet before treatment showed that all cardiac measurements were within normal limits; in fact, a few were less than normal.

REPORT OF CASES

CASE 1.—E. B., a white woman aged 36, a secretary, was first admitted to a hospital for mental disease on Oct. 6, 1929, with an illness diagnosed as dementia praecox, hebephrenic type. Insulin shock treatment was started on Jan. 19, 1938. The cardiac shadow at the beginning of treatment was 10.6 cm.; the blood pressure was 98 systolic and 56 diastolic. After forty-three days of treatment the heart measured 11.7 cm. and the blood pressure 114 systolic and 84 diastolic. At the end of seventy-nine days of treatment the cardiac shadow was 13.5 cm. and the blood pressure 112 systolic and 62 diastolic. Treatment was terminated on the ninety-second day, when the heart measured 13 cm., an increase of 22.6 per cent, and the blood pressure 114 systolic and 70 diastolic. The mental condition after treatment showed marked improvement, and the patient was permitted to go on an

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indefinite visit, whereas prior to treatment she could not be allowed out of the hospital. On the thirty-fifth day after treatment had ceased, the patient returned for reexamination. The cardiac shadow had decreased to 11.7 cm., and the blood pressure was 104 systolic and 74 diastolic. At that time it was noted that she was not maintaining her mental improvement. She showed more detachment, blocking and incoherence, although neither hallucinations nor delusions, which she had previously shown, were evident. Her mental condition eventually required return to the hospital. Eighty-five days after cessation of treatment the heart shadow measured 11.5 cm., and the blood pressure was 110 systolic and 74 diastolic. Although this patient was unable to maintain her mental improvement, her condition did not return to the level shown prior to treatment.

CASE 2.—B. B., a white woman aged 25, a stenographer, was first admitted to a hospital for mental disorders on Aug. 30, 1932, with an illness diagnosed as dementia praecox, hebephrenic type. Insulin shock therapy was begun on Jan. 19, 1938. The cardiac shadow at that time was 11.7 cm. and the blood pressure 100 systolic and 50 diastolic. After forty-three days the heart measured 12.3 cm. and the blood pressure 162 systolic and 92 diastolic. At the end of seventy-five days of treatment the cardiac shadow was 12.3 cm. and the blood pressure 124 systolic and 84 diastolic. Treatment was terminated on the eighty-second day, when the heart measured 12.5 cm., an increase of 6.8 per cent, and the blood pressure was 118 systolic and 72 diastolic. Moderate improvement was noted, so that the patient was allowed out of the hospital for week ends; prior to treatment this had been impossible. On the thirty-fifth day after treatment ceased, a roentgenogram showed a decrease in the cardiac shadow to 11.9 cm., with the blood pressure 106 systolic and 54 diastolic. It was also noted that the patient had failed to maintain her slightly improved state. She again became withdrawn from reality and occasionally reacted to auditory hallucinations. The patient could no longer be allowed out of the hospital. Eighty-eight days after cessation of the treatment the cardiac shadow measured 11.7 cm., and the blood pressure was 108 systolic and 74 diastolic. While the patient's mental condition showed some decline after the treatment stopped, it was still considered slightly improved as compared with that prior to treatment.

CASE 3.—C. B., a white woman aged 37, a missionary teacher, was first admitted to a hospital for mental disease on Jan. 23, 1928, with an illness diagnosed as dementia praecox, hebephrenic type. Insulin shock therapy was instituted on Jan. 19, 1938. On this date the cardiac shadow measured 12.2 cm. and the blood pressure 108 systolic and 64 diastolic. At the end of thirty-six days of treatment the cardiac shadow was 12.6 cm., with the blood pressure 104 systolic and 84 diastolic. After forty-five days of treatment the cardiac shadow had decreased to 11.8 cm., while the blood pressure was 118 systolic and 62 diastolic. This measurement represented a decrease of 3.3 per cent from the original findings. Treatment was terminated on the ninety-second day, with no further change in the cardiac shadow and no demonstrable improvement in the mental condition. Thirty-nine days after treatment was stopped the cardiac shadow was 13.2 cm., and the blood pressure was 100 systolic and 60 diastolic. On the eighty-ninth day after treatment ceased the cardiac measurement was 11.9 cm., and the blood pressure was 108 systolic and 66 diastolic. No change in the mental condition was noted.

CASE 4.—C. S., a white woman aged 39, a telephone operator, was first admitted to a hospital for mental disease on March 3, 1937, with an illness diagnosed as dementia praecox, paranoid type. Insulin shock therapy was instituted on Jan.

19, 1938, at which time the cardiac shadow measured 11.3 cm. and the blood pressure 100 systolic and 60 diastolic. After thirty-six days of treatment the heart measured 11.9 cm. and the blood pressure 104 systolic and 76 diastolic. At the end of forty-eight days of treatment, which had to be terminated because of a severe attack of acute pulmonary edema, the cardiac shadow measured 12.5 cm., an increase of 10.6 per cent, and the blood pressure was 116 systolic and 60 diastolic. At the cessation of treatment this patient showed moderate improvement in her mental condition. Auditory hallucinations were rare; delusions were not as evident, and blocking and incoherence were much improved. She appeared in better contact with reality. About a week after termination of treatment the patient became disturbed, violent and impulsive, whereas previously she had been calm, placid and self satisfied. Owing to the mental condition of the patient, it was impossible to make further roentgenographic observations until eight months after cessation of the treatment. At that time the cardiac shadow had decreased to 12 cm. and the blood pressure to 100 systolic and 60 diastolic.

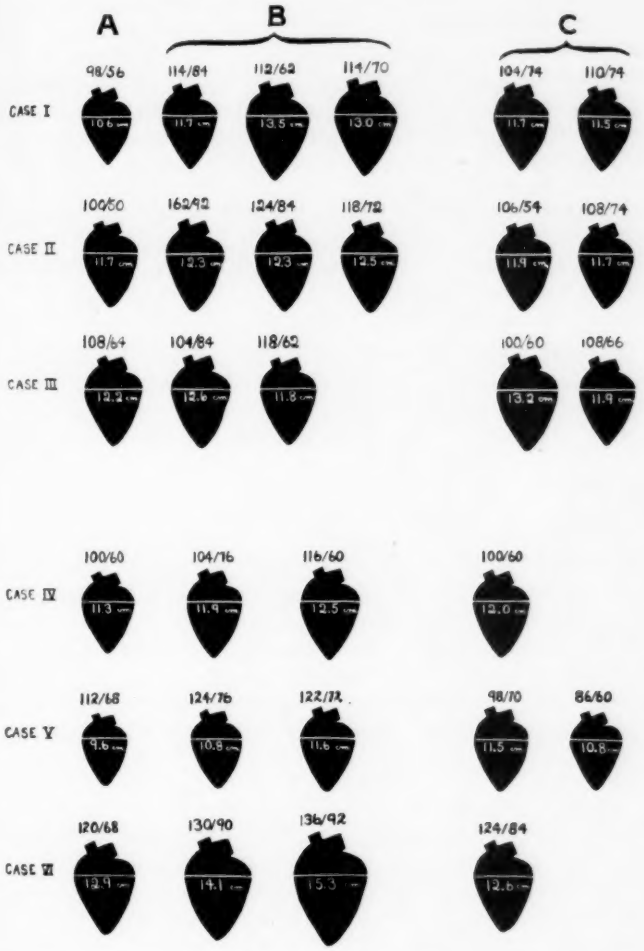
Case 5.—E. R., a white woman aged 37, a college professor, was first admitted to a hospital for mental disease on July 16, 1926, with an illness diagnosed as dementia praecox, paranoid type. Insulin shock therapy was started on Jan. 19, 1938, at which time the cardiac shadow measured 9.6 cm. and the blood pressure 112 systolic and 68 diastolic. After forty-three days of treatment the cardiac measurement was 10.8 cm. and the blood pressure 124 systolic and 76 diastolic. At the end of seventy-nine days of treatment the cardiac measurement was 11.6 cm., an increase of 20.8 per cent, and the blood pressure was 122 systolic and 72 diastolic. Treatment was terminated on the ninety-second day, with no further change in the cardiac measurements or in the mental condition. On the thirty-ninth day after cessation of treatment the cardiac shadow measured 11.5 cm., and the blood pressure had decreased to 98 systolic and 70 diastolic. A roentgenogram taken on the one hundred and twenty-first day after measurement showed that the measurement of the cardiac shadow had decreased to 10.8 cm. and the blood pressure to 86 systolic and 60 diastolic. No improvement in the patient's mental condition could be noted.

Case 6.—C. M., a white man aged 30, an osteopathic practitioner, was first admitted to a hospital for mental disease on March 14, 1935, with an illness diagnosed as dementia praecox, paranoid type. Insulin shock therapy was started on May 19, 1938, at which time the cardiac shadow measured 12.9 cm. and the blood pressure 120 systolic and 68 diastolic. On the forty-ninth day of treatment the measurement had increased to 14.1 cm. and the blood pressure to 130 systolic and 90 diastolic. At the end of eighty-nine days treatment was terminated; the cardiac shadow measured 15.3 cm., an increase of 18.5 per cent, and the blood pressure was 136 systolic and 92 diastolic. There was marked improvement in the mental condition. On the eighty-first day after treatment ceased a roentgenogram showed that the cardiac shadow had decreased to 12.6 cm. and the blood pressure to 124 systolic and 84 diastolic. The mental condition during this period showed a slight decline, which, however, was not as marked as that in case 1.

Comment.—The accompanying chart summarizes diagrammatically the changes in size of the cardiac shadow in each case, together with the blood pressure findings. Although it is evident that the number of cases is too small to permit formal deductions, the facts appear sufficiently consistent to show that insulin shock therapy produces changes in the cardiovascular system as well as in the

mental condition of patients undergoing this treatment. As patients with disease of relatively long standing were used in the study, improvement could not be expected in a high percentage of cases.

In spite of such rigorous treatment, all patients showed marked improvement in their physical condition. Gains in weight, varying from 17 to 28 pounds (7.7 to 12.7



Changes in transverse measurements of the heart in routine roentgenograms taken at a distance of 7 feet before (*A*), during (*B*) and after (*C*) insulin treatment. Changes in blood pressure are also shown in the chart.

Kg.), were noted in all cases. Normal menstrual periods were established in a patient who had had amenorrhea for over a year. Another patient became quiet during her periods, whereas previously she had been disturbed, assaultive and destructive at those times. These observations may indicate some favorable readjustment of the endocrine system. Moderately severe acne vulgaris showed

improvement almost at once in 2 cases. The appetite in all cases improved. During the treatment daily determinations of blood pressure showed rises of from 20 to 30 mm.

The changes in measurement of the cardiac shadows are of considerable interest when compared with the degree of improvement. In cases 1 and 6 marked increases of 22.6 and 18.5 per cent, respectively, were noted in the size of the heart shadow. Both patients showed marked improvement in the mental condition. However, the improvement was not maintained in either case after cessation of the treatment. In cases 2 and 4, in which moderate improvement was noted, increases of 6.8 and 10.6 per cent, respectively, were noted in the size of the cardiac shadow. In cases 3 and 5 no improvement was shown in the mental condition. While in case 3 there was an actual decrease of 3.3 per cent in the size of the cardiac shadow, in case 5 there was an unexplained increase of 21 per cent. As the blood pressure increased simultaneously with the increase in size of the heart, one may conclude that there was hypertrophy rather than dilatation of the heart, and therefore that circulation would be improved. In all cases the cold, clammy, cyanotic extremities showed marked improvement, and a healthy color returned to the lips and cheeks.

GENERAL COMMENT

For a considerable period, investigators have called attention to the inadequacy of the circulatory system and its functions in persons suffering from dementia praecox. Lewis,[1] in studying the constitutional factors in dementia praecox, with particular attention to the circulatory system, found that in a group of 601 patients with the disease 430 had hearts of less than average weight and 171 hearts of average weight or above. He showed that this was not true in other psychoses. He concluded that the heart not only had been arrested in development but lacked ability to react with satisfactory compensatory hypertrophy when the occasion demanded, and often remained below the average size and weight after development of valvular insufficiencies. Freeman, Hoskins and Sleeper [2] found that in 180 schizophrenic patients the mean systolic blood pressure was 11.2 mm. lower than that of normal control subjects, and that the mean diastolic pressure of the patients was 16.7 mm. below that of the controls. Freeman [3] also compared the arm to carotid circulation time for 73 schizophrenic patients with that for a group of normal control subjects. He found that schizophrenia was characterized by abnormal slowing of the circulation time and that there was an abnormally high intraindividual variability in the rate of flow. Freeman [4] repeated this work under basal conditions and concluded that, on the average, schizophrenic patients have an abnormally slow and a highly variable rate of blood flow. Other investigators have found the circu-

1. Lewis, N. D. C.: The Constitutional Factors in Dementia Praecox, Nervous and Mental Disease Monograph 35, Washington, D. C., Nervous and Mental Disease Publishing Company, 1923.

2. Freeman, H.; Hoskins, R. G., and Sleeper, F. H.: The Blood Pressure in Schizophrenia, Arch. Neurol. & Psychiat. **27**:333-351 (Feb.) 1932.

3. Freeman, H.: The Arm-to-Carotid Circulation Time in Normal and Schizophrenia Subjects, Psychiatric Quart. **8**:290-299 (April) 1934.

4. Freeman, H.: Variability of Circulation Time in Normal and in Schizophrenia Subjects, Arch. Neurol. & Psychiat. **39**:488-493 (March) 1938.

lation time of schizophrenic patients to be normal.[5] The cardiovascular system of schizophrenic patients was studied by Linton, Hamilink and Hoskins,[6] using the Schneider method. This test [7] purports to afford a measure of cardiovascular "fitness." When it was applied to 99 schizophrenic patients and 25 normal control subjects, the score indicated a significant lowering of physiologic fitness in the schizophrenic patients. However, the authors expressed the belief that the test mirrored the degree of physical activity rather more than the intrinsic degree of normality.

A deficiency in oxygen metabolism has also been recognized in schizophrenic patients. McFarland [8] has pointed out that deficiencies in oxygen assimilation may bring about in nonpsychotic subjects a chain of symptoms that are highly suggestive of those observed in schizophrenia. Hoskins [9] who studied a group of 214 schizophrenic patients, concluded that schizophrenia is characterized, among other physiologic abnormalities, by downward displacement of the rate of oxygen consumption. In reviewing the results of ten years' research at the Worcester State Hospital, the same author [10] concluded that defective oxygen metabolism is an important factor in the schizophrenic psychosis. That adequate oxidation depends on an adequate circulatory system must be granted. Therapeutic procedures that tend to increase the efficiency of cardiac and circulatory functions, if successful, would tend to aid in oxygen metabolism. Thompson and Corwin,[11] by the use of daily vigorous physical exercise in 26 cases of schizophrenia, improved the circulation, as evidenced by an increase in blood pressure and relief of cyanosis of the extremities, together with improvement of the cold, clammy extremities so often seen. In their cases the color of the cheeks was better, there was gain in weight and the mental condition was much improved.

As the autonomic nervous system has a direct effect on the circulatory apparatus, its role must not be neglected. Hoskins and Jellinek [12] suggested that in schizophrenic patients the hydrostatic forces of the circulatory processes are less modified by neurogenic factors, owing

5. Finesinger, J. E.; Cohen, M. E., and Thomson, K. J.: Velocity of Blood Flow in Schizophrenia, Arch. Neurol. & Psychiat. **39**:24 (Jan.) 1938.

6. Linton, J. M.; Hamilink, M. H., and Hoskins, R. G.: Cardiovascular System in Schizophrenics Studied by Schneider Method, Arch. Neurol. & Psychiat. **32**:712-722 (Oct.) 1934.

7. Schneider, E. C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

8. McFarland, R. A.: The Psychological Effect of Oxygen Deprivation (Anoxemia) on Human Behavior, Arch. Psychol., 1932, no. 145.

9. Hoskins, R. G.: Oxygen Consumption (Basal Metabolic Rate) in Schizophrenia, Arch. Neurol. & Psychiat. **28**:1346-1364 (Dec.) 1932.

10. Hoskins, R. G.: Oxygen Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **38**:1261-1270 (Dec.) 1937.

11. Thompson, J. W., and Corwin, W.: Treatment of the Total Organism in Schizophrenic Patients, Am. J. Psychiat. **95**:1059-1066 (March) 1939.

12. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Psychologic and Organic Concomitants, A. Research Nerv. & Ment. Dis., Proc. **14**:211, 1933.

possibly to diminution in the activity of the sympathetic nervous system. From a study of 50 schizophrenic and 25 normal subjects, Krinsky and Gottlieb [13] concluded that the autonomic reactions of the schizophrenic patient were less facile than normal. Gellhorn,[14] in reviewing a large amount of literature on the action of hypoglycemia on the central nervous system, concluded that in schizophrenia there was hypofunction of the sympathetic nervous system, and that improvement or cure may be brought about by sufficient stimulation of this system. He has shown that oxygen deficiency in inspired air stimulates the sympathetic system. It is now accepted that insulin acts by reducing the oxidative processes of the brain cells.

The effect of insulin on the heart has been studied by others. Hadorn,[15] by use of the electrocardiograph, showed that during hypoglycemia changes appeared that indicated a lesion of the heart, or at least temporary involvement of its function. While no electrocardiographic evidence of cardiac lesions could be found one week after the course of treatment was stopped, Hadorn expressed the belief that this reversibility did not indicate harmlessness. Lakosin [16] reported that with physical improvement orthocardiographic studies demonstrated a change in the heart from the vertical position, characteristic of persons with dementia praecox, to the dorsal position, characteristic of the pyknic person. Lauter and Baumann [17] proved, by the use of the acetylene method, that during hypoglycemic coma there is an increase in cardiac activity; they calculated an increase in cardiac output of up to 30 per cent per beat and 50 per cent per minute. Ernstene and Altschule,[17] as well as Alzona,[17] have confirmed these results, using the same method.

It appears that during hypoglycemic shock physical symptoms suggestive of sympathetic stimulation are in the foreground, namely, sweating, dilatation of the pupils, rise in blood pressure, increase in heart rate, motor agitation and, potentially, a massive catabolic discharge of energy in the form of convulsions. It seems reasonable, therefore, to regard the changes in the cardiac measurements and cardiovascular functions accompanying the alterations in the mental condition as due in large measure to the direct effect of sympathetic stimulation. These mental and physical changes appeared to subside after the withdrawal of the source of stimulation in that gains in the mental condition were not maintained and measurements of the cardiac shadow decreased

13. Krinsky, C. M., and Gottlieb, J. S.: Peripheral Venous Blood Pressure in Schizophrenia and in Normal Subjects, Arch. Neurol. & Psychiat. **19**:304 (Feb.) 1936.

14. Gellhorn, E.: The Action of Hypoglycemia on the Central Nervous System, J. A. M. A. **110**:1433 (April 30) 1938.

15. Hadorn, W.: Untersuchungen des Herzens en hypoglykämischer Schock, Arch. f. Krieslaufforsch. **2**:70, 1937.

16. Lakosin, cited by Krasnushkin, E. K., and Khanlaryan, A. K.: Insulin Shock Therapy of Schizophrenia, Sovet. psikhonevrol. **13**:5, 1937; abstracted, Arch. Neurol. & Psychiat. **41**:209 (Jan.) 1939.

17. Cited by Beiglböck, W.: Der hypoglykämische "Schock," Wien. klin. Wchnschr. **51**:497 (May 6) 1938.

nearly to the original figures. The systolic and diastolic blood pressures appeared to increase and decrease with similar changes in the cardiac shadow, although to a lesser degree.

SUMMARY AND CONCLUSIONS

In 5 of 6 schizophrenic patients submitted to insulin shock therapy, there occurred during treatment a measurable enlargement of the cardiac shadow and an increase in systolic and diastolic blood pressure.

In 2 cases in which there was marked improvement in the mental condition there were increases in the size of the heart shadow of 22.6 and 18.5 per cent at the end of the ninety-second and eighty-ninth days of treatment, respectively. In 2 cases in which there was moderate improvement there were increases of 6.8 and 10.6 per cent in the measurement of the heart shadow at the end of ninety-two and forty-eight days of treatment, respectively. In 1 case in which there was no mental improvement the measurement of the heart shadow showed a decrease of 3.3 per cent at the end of forty-eight days of treatment, while in another case in which there was no mental improvement, the measurement of the heart was increased 20.8 per cent at the end of seventy-nine days of treatment.

In all cases measurements of the heart were made at various intervals after cessation of treatment; these showed reduction in the heart shadow to a size approaching that prior to treatment. Coincidently it was observed that the favorable therapeutic effects at the end of the treatment failed to be maintained.

It is suggested that some of the mental improvement and cardiovascular changes associated with insulin shock therapy may be explained by stimulation of the sympathetic nervous system. It appears that when the therapeutic stimulation of the sympathetic system ceased, its favorable effects on the mental condition and the cardiovascular system of the patients gradually subsided.

MONOCHOREA AND SOMATOTOPIC LOCALIZATION

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The limitation of choreic movements to one extremity is rarely observed clinically, and of such cases even fewer have been described pathologically. A careful search of the literature reveals only 1 clearcut clinical instance of monochorea, reported by Münzer.[1] The case to be presented is significant because of the selectivity of the lesion, and therefore contributes to the problem of somatotopic localization within the striatum.

REPORT OF A CASE

History.—H. G., a married woman aged 41, born in Austria, was admitted to the Montefiore Hospital on Aug. 29, 1937, because of chronic rheumatic cardiovascular disease. For many years prior to admission she had suffered from moderate dyspnea on exertion and mild pitting edema of the ankles. In February 1937 auricular fibrillation was noted. In April 1937 she complained of a tired feeling and went to bed. A few minutes later she was found to be drowsy, with paralysis of the left arm and leg and left supranuclear facial paresis. Motor power of the arm and leg returned almost completely within a short period. In July 1937 spontaneous, patternless, purposeless movements of the left forearm and hand appeared; these involuntary movements became progressively more marked. A history of frequent gallbladder attacks was obtained. Tonsillectomy had been performed in 1925.

General Examination.—The patient was well developed and well nourished. Cardiac examination revealed enlargement of the heart to the left, auricular fibrillation, with a deficit in the pulse rate of 28, an apical diastolic murmur, systolic and diastolic murmurs at the base and accentuation of the second pulmonic sound. There was moderate tenderness in the region of the right subcostal margin; the liver and the spleen were not palpable.

Neurologic Examination.—The gait was normal except for slight dragging of the left foot. There were spontaneous, irregular, patternless, purposeless movements on the left side, involving the muscles of the neck, shoulder, arm, forearm and hand. The dyskinesia presented fragments of choreiform, myoclonic, athetotic and dystonic movements, the choreic being predominant. These involuntary movements were aggravated by emotional stress; they ceased during sleep. The fingers of the left hand remained almost constantly in hyperextension. Muscle tonus in the left upper extremity alternated between hypertonia and hypotonia. On the left side there was a defective arm swing, and a pronator sign was suggested.

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Read at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 6, 1939.

1. Münzer, F. T.: Choreatische Syndrom der rechten oberen Extremität als Ausdruck einer monosymptomatischen Lues cerebri, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:12, 1935.

The finger to nose test was performed poorly on that side. Muscular strength in the lower and upper limbs was normal on the left side but the deep tendon reflexes were slightly exaggerated on that side. The only pathologic reflex was a Chaddock's sign on the left. Sensory examination gave normal results. The pupils reacted well to light and in accommodation. There was weakness of the left side of the face of supranuclear type, more marked on mimetic innervation. Mentally, the patient was somewhat depressed, showed emotional instability and once expressed suicidal ideas. Memory and orientation were good. There was some defect in attention, but this was probably caused by middle ear deafness. She had frequent attacks of spasmodic crying, often produced by what did not appear to be adequate stimuli. During her stay in the hospital, with adjustment, her depression became less and less marked.

Laboratory Data.—Examination of the blood and spinal fluid and blood chemical determinations gave normal results. On admission the urine was normal, but on September 16 it gave a 4 plus reaction for albumin and was loaded with red blood cells. Roentgen examination of the heart disclosed elongation of the left ventricle, horizontal enlargement of the left auricle and enlargement of the right auricle. The electrocardiogram revealed right axis deviation and auricular fibrillation. Blood cultures on several occasions were sterile.

Course.—On September 16 cystitis was noted. Later, signs of pulmonary, splenic and renal infarction appeared. The neurologic picture remained unchanged. The abnormal involuntary movements spared the face and the left lower extremity until the end. Bronchopneumonia developed, and the patient died on Feb. 24, 1938.

Gross Examination.—Brain: A small area of softening was noted at the tip of the right temporal pole. The brain was cut coronally. In sections through the anterior part of the lateral ventricles small areas of softening involved the superior border of the right caudate nucleus and putamen and the gray matter of the right third orbital convolution. These areas of softening were slightly cystic. The right anterior horn of the lateral ventricle was slightly more dilated than the left. In sections through the oral end of the pallidum the area of softening involved the upper third of the putamen and caudate nucleus; the internal capsule appeared normal. The right insula in this region was also partially destroyed. In sections at about the middle of the thalamic nuclei the area of softening had disappeared, but destruction around the insula was still visible. In sections through the corpus Luysi and red nucleus no abnormalities were noted.

Spinal Cord: Sections of the cord appeared normal.

Microscopic Examination.—Coronal sections from the beginning to the end of the striatum were embedded in pyroxylin, cut serially and stained by the myelin sheath and cresyl violet methods. Additional sections from various cortical areas and through the red nucleus, pons, cerebellum, medulla oblongata and spinal cord were studied by the same methods.

Striatum and Pallidum: The anterior horn of the right ventricle was slightly dilated. At about 2.5 mm. from the oral end of the caudate nucleus a small area of softening, measuring 2 by 3.5 mm., was situated at the superior part of the right caudate nucleus (fig. 1). Part of the white matter on the superolateral border of the caudate nucleus was partially demyelinated. The area of softening was largest at a distance of 1 cm. from its oral end. At this level the entire caudate nucleus was shrunken, and one fifth contained a cystic area of softening, measuring 2.5 by 3.5 mm. The putamen made its appearance 5 mm. from the beginning of the area of softening in the caudate nucleus, and on its superolateral

border there was a small cyst, measuring 1.5 by 1.5 mm. (fig. 2). This cyst, measuring 5 by 3 mm., became largest at a distance of 6 mm. from the oral end of the putamen. At this level there was also partial destruction of the superior surface of the insula, and the area of softening in the caudate nucleus became smaller, measuring 3 by 2.5 mm. Throughout these sections the internal capsule appeared intact, except for a few fibers bordering the caudate nucleus (figs. 1 to 3). At 11 mm. from the oral end of the putamen the softening in the caudate nucleus became smaller, whereas the cystic area in the putamen appeared somewhat larger, measuring 3 by 7 mm. In a section passing through the beginning of the globus

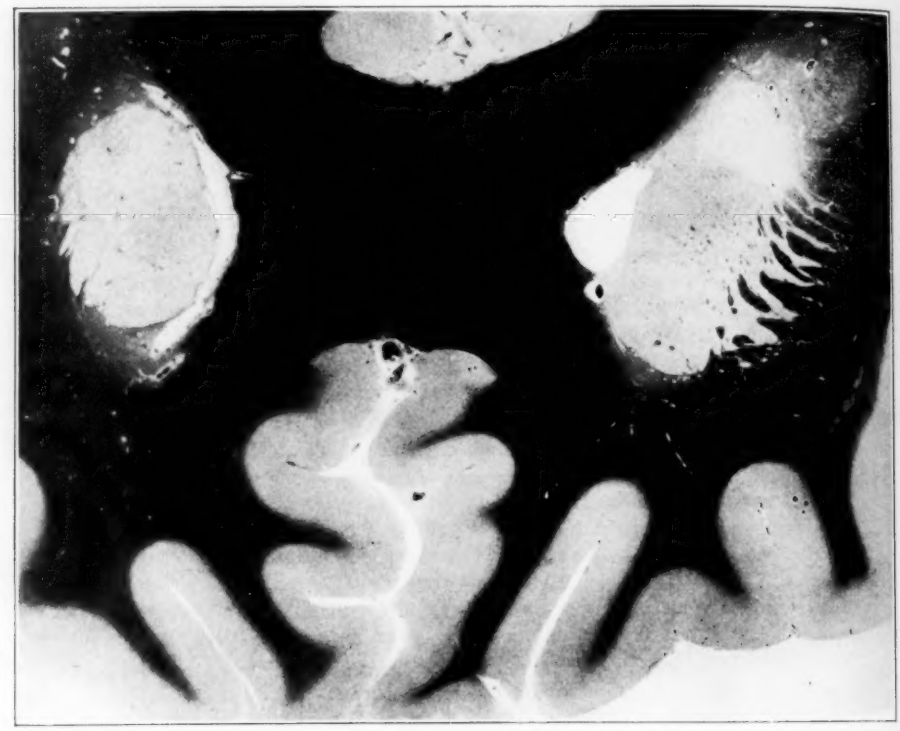


Fig. 1.—Coronal section through the striatum at about 2.5 mm. from the oral end of the caudate nucleus, showing destruction of the superior part of the right caudate nucleus and partial demyelination of the white matter near it. Myelin sheath stain.

pallidus the same process was noted (fig. 3). In sections 13 mm. from the oral end of the putamen the area of softening in the island of Reil was more marked, and the fibers of the external capsule were pale; the claustrum was spared. The area of softening in the caudate nucleus was smaller; that in the putamen remained unchanged. In sections 14 mm. from the oral end of the putamen the area of softening extended throughout its upper third and measured 1 cm. by 3 mm. The fibers of the external capsule and part of the superior fibers of the internal capsule stained poorly. The insula showed a greater amount of destruction. In sections passing through the anterior commissure the same process was noted, except that

the area of softening in the caudate nucleus was smaller (fig. 4). The right pallidum stained less deeply than the left. The destruction of the island of Reil and of the claustrum became greater. The fibers of the internal capsule bordering the putamen were intact; those near the caudate stained poorly (fig. 4). The area of softening in the caudate nucleus disappeared at a level of 23.5 mm. from its oral end. In sections through the thalamic nuclei, 18 mm. from the oral end of the putamen, the caudate nucleus and the putamen were shrunken; the right caudate nucleus was about half the size of the left. There was an insular area of destruction in the upper third of the right putamen. The external capsule stained



Fig. 2.—Coronal section through the striatum, disclosing dilatation of the right lateral ventricle and destruction of the upper third of the right caudate nucleus and upper fifth of the right putamen. There is slight demyelination of the neighboring white matter. Myelin sheath stain.

poorly, and the right island of Reil was partially destroyed. The second and particularly the first segment of the right globus pallidus were slightly shrunken and stained poorly. The fibers of the superior pole of the internal capsule bordering the caudate nucleus also stained poorly. At 19 mm. from the oral end of the putamen the caudate nucleus and the putamen appeared shrunken. There was a small area of destruction in the superior part of the putamen, with involvement of the structures enumerated in the previous sections; the pallidal segment stained poorly. At 20 mm. from the oral end of the putamen the area of softening in the putamen disappeared, but the caudate nucleus and the putamen were shrunken

and pale and the pallidal segment stained poorly. At this level and for a distance of 2 mm. more there was involvement of the internal capsule and superior portion of the island of Reil; the right ansa lenticularis was slightly shrunken. In sections through the third ventricle, 24 mm. from the oral end of the putamen,



Fig. 3.—Coronal section passing through the beginning of the right globus pallidus, showing shrinkage of the caudate nucleus, destruction of its upper fourth and of the upper third of the putamen and slight demyelination of some fibers of the internal capsule near the superior surface of the caudate nucleus. The cavity at the inferior border of the caudate nucleus is a dilated venous channel. Myelin sheath stain.

there were destruction of the island of Reil and shrinkage of the right caudate nucleus and putamen and part of the pallidum. The pallidal fibers on the right stained poorly as compared with those on the left. The outer segment of the putamen had a few lacunas, and there was slight demyelination of the superior border of the fibers in the internal capsule. At 25 mm. from the oral end of the putamen there were shrinkage and pallor of the caudate nucleus and putamen,



Fig. 4.—Coronal section through the anterior commissure, showing destruction of the upper fourth of the right caudate nucleus and putamen, pallor of the outer portion of the globus pallidus and demyelination of the fibers of the white matter and of the internal capsule near the caudate nucleus.

pallor of the pallidal segments and of the inferior fibers of the internal capsule, thinning of the ansa lenticularis and partial destruction of the island of Reil. In sections passing through the most anterior part of the red nucleus there were shrinkage and pallor of the caudate nucleus and putamen and partial destruction of the insula; the internal capsule, red nucleus, corpus Luysi, zona incerta and thalamic nuclei were normal (fig. 5).

In cresyl violet preparations the areas of softening appeared to consist of cysts, some of which were completely empty; others contained debris and a few compound granular corpuscles. The borders of the cysts contained a few compound granular corpuscles, proliferating vessels, astrocytes, a few fibroblasts and glia fibers. The vessels showed no evidence of atherosclerosis. There was no inflammatory reaction. The ganglion cells of the right caudate nucleus and putamen near these cysts showed pathologic changes, such as complete disintegration, pallor, fantom-like appearance and ischemia. Occasional neuronophagia and



Fig. 5.—Coronal section through the red nucleus and corpus Luysi on the right, showing shrinkage and pallor of the caudate nucleus and putamen and destruction of part of the island of Reil. The red nucleus and corpus Luysi are intact. Myelin sheath stain.

satellitosis were also noted. In the island of Reil were partial destruction and distortion in the arrangement of the cytoarchitectural layers. The various cortical layers were replaced by compound granular corpuscles and proliferating vessels. The ganglion cells showed all types of pathologic changes. Sections from the right third orbital convolution and from the tip of the temporal pole showed the same pathologic process as in the island of Reil. The other cortical convolutions were normal.

Pons: The brachium conjunctivum and other pontile structures were normal.

Other Regions: Sections through the cerebellum and the dentate nuclei, the medulla oblongata and the spinal cord were normal. The pyramidal pathways throughout these sections were intact.

COMMENT

The choreic movements of this patient were spontaneous, patternless, purposeless and unilateral and involved the groups of muscles on the left side of the neck and the left shoulder, arm, forearm and hand. There was slight motor deficit of this extremity, as evidenced by the hyperactive tendon reflexes. The contralateral choreiform movements and the impairment in associated movements, limited to the left upper extremity, were unquestionably caused by the lesion in the oral and superior parts of the right caudate nucleus and putamen; the slight motor deficit was the result of the small lesion in the right internal capsule.

The lesion in the caudate nucleus began at about 2.5 mm. from the oral end of the nucleus and extended for a distance of from 21 to 23.5 mm. In the putamen the lesion extended for a distance of 20 mm. In coronal sections the length of the caudate nucleus in the anteroposterior diameter was 5.8 cm. and that of the putamen 4.7 cm. The lesion, therefore, occupied a little more than one third of these structures, the putamen being slightly more involved than the caudate nucleus. In the latter the area of destruction was limited to its superior part, involving the lateral and mesial surfaces; in the putamen the superior and lateral surfaces were affected.

Somatotopic localization in the striatum has never been proved conclusively. Such a possibility, however, was suggested by Mingazzini [2] and the Vogts.[3] Although cases of dystonia confined to the muscles of the neck were reported by Cassirer and Bielschowsky,[4] Alpers and Drayer [5] and us,[6] the pathologic changes described in these instances were not limited to a specific area of the striatum. It is well known that somatotopic localization is present not only in the motor and sensory systems but also in other systems (cerebellum). Although experimental and adequate pathologic proof is lacking at present, there is reason to suppose that a similar somatotopic localization exists in the extrapyramidal system. From the clinical and histopathologic observations in this case, it may be postulated that the various parts of the body are represented segmentally in the striatum, the extreme oral pole being associated

2. Mingazzini, G.: Das Linsenkernsyndrom, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:25, 1912.

3. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, Leipzig, Johann Ambrosius Barth, 1920.

4. Cassirer, R., and Bielschowsky, M.: Halsmuskelkrampf und Torsionspasmus, Klin. Wchnschr. **1**:53, 1922. Bielschowsky, M.: Ueber den Status marmoratus des Striatums und atypische Markfaser geflechte der Hirnrinde, J. f. Psychol. u. Neurol. **31**:125, 1924.

5. Alpers, B. J., and Drayer, C. S.: The Organic Background of Some Cases of Spasmodic Torticollis: Report of a Case with Autopsy, Am. J. M. Sc. **193**:378, 1937.

6. Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **39**:939 (May) 1938.

with movements of the muscles of the head and face, the middle part with those of the upper extremity and trunk and the caudal part with those of the lower extremity. From our case it might further be inferred that the upper extremity is represented in the superior part of the caudate nucleus and the superolateral surface of the putamen, a position somewhat analogous to that of the representation of the upper extremity in the internal capsule.

The selectivity of the lesion in this and other instances suggests that disease of the striatum is closely linked with the release of involuntary movements. It should be mentioned that we observed a number of cases in which there were no involuntary movements and lesions of the corpus striatum were present. In most of those cases, however, there were also lesions of the internal capsule. Wilson [7] suggested that for the occurrence of choreic movements it is necessary to have a relatively intact corticospinal tract. The relative sparing of the internal capsule in the instance reported here may account for the appearance of monochorea, while in many other instances the absence of involuntary movements was the result of the lesion in the pyramidal pathways. We have observed a number of clinical cases in which there were involuntary movements which disappeared after a lesion of the pyramidal tract; recently, such instances were confirmed histopathologically by one of us. This, however, does not mean that the lesion must be limited to the striatum. Lesions anywhere along the striatal pathways may lead to similar involuntary movements. Experimental lesions in the striatum (Wilson,[7] Delmas-Marsalet [8]) have so far failed to produce symptoms similar to those seen in chorea. Bonhoeffer,[9] in 1897, described a case of chorea with involvement of the superior cerebellar peduncles. Such cases have not been reported since, and a careful review of his case disclosed lesions in other parts of the nervous system. Choreiform movements were absent in a series of cases of lesions of the superior cerebellar peduncles reported by Davison, Goodhart and Savitsky.[10] Experimental lesions of the superior cerebellar peduncles produced by Ferrier and Turner [11] and Ferraro and Barrera [12] failed to produce choreic movements.

In our case there were also a lesion of the right insula of Reil and insignificant lesions in the temporal pole and third orbital convolution

7. Wilson, S. A. K.: Involuntary Movements and Their Pathogenesis: Chorea and Athetosis, in Modern Problems in Neurology, New York, William Wood & Company, 1929.

8. Delmas-Marsalet, P.: Functions de noyau caude, Bordeaux, Y. Cadoret, 1925.

9. Bonhoeffer, K.: Ein Beitrag zur Lokalisation der choreatischen Bewegungen, Monatschr. f. Psychiat. u. Neurol. **1**:6, 1897.

10. Davison, C.; Goodhart, S. P., and Savitsky, N.: The Syndrome of the Superior Cerebellar Artery and Its Branches, Arch. Neurol. & Psychiat. **33**: 1143 (June) 1935.

11. Ferrier, D., and Turner, W. A.: A Record of Experiments Illustrative of the Symptomatology and Degenerations Following Lesions of the Cerebellum and Its Peduncles and Related Structures in Monkeys, Proc. Roy. Soc., London **54**:476, 1893.

12. Ferraro, A., and Barrera, S. E.: The Effects of Lesions of the Superior Cerebellar Peduncle in the Macacus Rhesus Monkey, Bull. Neurol. Inst. New York **5**:165, 1936.

on the same side. It is doubtful whether these lesions had any clinical significance. They may have been associated with some of the mild mental changes, and possibly with the pathologic crying. The latter, however, as demonstrated by Davison and Kelman,[13] may have been the result of the lesions in the striatum.

As the lesion in our case was of embolic origin, it may be advisable to review briefly the vascular supply of the striatum. The head of the caudate nucleus and the anteromedial portion of the putamen are supplied by the anteromedial basal branches of the anterior cerebral artery; part of the head of the caudate nucleus and the anterolateral part of the putamen are supplied by the medial striate arteries, branches of the middle cerebral artery, while the tail of the caudate nucleus, the posterior portion of the putamen and the amygdaloid nucleus are supplied by the choroid branch of the internal carotid artery and branches from the lenticulostriate artery. A careful review of the pathologic changes in our case shows that the lesion involved the superolateral part of the putamen and part of the head of the caudate nucleus, which is supplied by the medial striate arteries, branches of the middle cerebral artery.

A careful survey of the literature discloses only 1 instance of monochorea of the right upper extremity (that of Münzer [1]) and in this case the condition followed cerebral syphilis. In Münzer's,[1] as in our case, the monochorea was associated with facial weakness for mimetic movements and slight pyramidal tract signs. In Münzer's case autopsy was not performed. Fragnito and Scarpini [14] reported a case of hemichorea in which, in addition to the disturbance in the upper extremity, there was slight involvement of the lower extremity. They observed a lesion in the right striatum, lying chiefly in the medial portion of the putamen, extending posteriorly along the external medullary lamina and forward, close under the anterior border of the internal capsule, to affect slightly the head of the caudate nucleus.

In hemiballismus, which is usually the result of a lesion of the corpus Luysi, it has been assumed by von Santha [15] and Martin and Alcock [16] that lesions of the anteromedial or oral pole are associated with involuntary movements of the face, lesions of the middle part with the upper limb and lesions of the posterior portion with the lower limb. These assumptions were based on the fact that in these cases the hemiballismus spared the facial muscles and that the corresponding oral pole of the corpus Luysi was intact. In our case of monochorea, in which the face was not involved, the most anterior portion of the caudate nucleus was spared; however, at the tip of the putamen a minute lesion was observed (figs. 1 and 2). The posterior parts of the caudate nucleus and putamen

13. Davison, C., and Kelman, H.: Pathologic Laughing and Crying, Arch. Neurol. & Psychiat. **42**:595 (Oct.) 1939.

14. Fragnito, O., and Scarpini, V.: Reperto anatomo-patologica in un caso di emicorea simtomatica, Riv. di pat. nerv. **31**:524, 1926.

15. von Santha, K.: Zur Klinik und Anatomie des Hemiballismus, Arch. f. Psychiat. **84**:665, 1928.

16. Martin, J. P., and Alcock, N. S.: Hemichorea Associated with Lesions of the Corpus Luysii, Brain **57**:504, 1934.

in our case were intact, the absence of choreic movements in the lower extremity being thus accounted for. As with lesions of the pyramidal system, the choreic movements involve the muscles of the extremity on the side contralateral to the lesion in the striatum.

It is well known, as shown by Wilson,[17] Weil [18] and others, that in a number of cases of chorea or hemichorea the lesions were not limited to the striatum, but were present in the cerebellostriopallidothalamomesencephalic system or pathways. A lesion anywhere along this system may produce involuntary movements. It is our opinion that not all of the so-called choreic movements belong to this group and that an attempt should be made to differentiate some of these movements from the classic form of chorea. This is especially true of hemiballismus. A number of cases of hemiballismus described in the literature in which there were an intact striatum and lesions in the corpus Luysi have at times been labeled instances of hemichorea. A review of a number of our cases of hemiballismus demonstrated that the involuntary movements in such cases differed from those seen in chorea in that they consisted of massive, violent, flinging movements of one extremity or one half of the body. Martin and Alcock,[16] who analyzed cinematograms of the movements in chorea and in hemiballismus, expressed the opinion that there is no difference between them, except in the violence of the movements, i. e., "a difference of degree and not of quality." As further proof of this, they [16] stated that they observed similar violent movements in cases of Huntington's chorea. It is our opinion that the difference in the "degree" of these movements depends on which structures are involved. We have not seen such violent movements in cases of chorea in which the corpora Luysi or their connections with the pallidum were spared. With pure lesions of the corpus Luysi, as noted in 2 of our cases and in those reported in the literature, these movements are always massive and violent, have a definite design, are repetitive and involve all the muscles of one extremity or of one half of the body, whereas in chorea the movements vary, are not as violent and do not occur simultaneously in all muscles of the extremity or the body, and the arc described is smaller. When massive movements appear in chorea it should be suspected that there is additional involvement of the corpus Luysi or its connecting pathways.

CONCLUSION

In a case of monochorea limited to the right upper extremity which was observed clinically a partial lesion of the caudate nucleus and putamen was disclosed.

From the observations in our case it may reasonably be postulated that somatotopic localization exists in the striatum. The extreme oral pole is associated with movements of the muscles of the head and face, the middle with those of the upper extremity and trunk and the caudal with those of the lower extremity.

17. Wilson, S. A. K.: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427, 1913-1914.

18. Weil, A.: A Contribution to the Pathology of Hemichorea, Brain **51**:36, 1928.

DISCUSSION

DR. ARTHUR WEIL, Chicago: In presenting this interesting case as a confirmation of the theory of somatotopic localization within the striate body, as taught by C. and O. Vogt and by Mingazzini, one should not neglect other possibilities of explanation and theories which are based on physiologic observation and phylogenetic studies rather than on anatomic considerations alone. Kleist assumed that the globus pallidus was the center of synergistic regulation of mass movements of the muscles of the axis and of the proximal joints. The periphery of the extremities and the automatisms of speech and mimic expression were represented in the neostriatum.

In the present case the absence of choreic movements in the face may easily be explained by the facial paralysis: Since no intentional movements of those muscles were possible, they could not, of course, be contracted by the interference of a choreic movement. Dr. Davison explained the absence of choreic movements in the legs by the fact that the posterior third of the neostriatum was spared. However, in a case of hemichorea which I described in 1928 only the head of the caudate nucleus was destroyed by a hemorrhage, and yet choreic movements were spread all over the contralateral side. Many neurologic laboratories have in their collections brains with hemorrhages in exactly the same region from patients in whom hemichorea never developed. In other cases of hemichorea, described by C. and O. Vogt, by Lloyd and Winkelman and by myself, there was, besides the localized vascular lesion, hemiatrophy of the striatum or involvement of the thalamus and the body of Luys. It is suggestive, therefore, to assume that accessory conditions like these must precede or must be superimposed on the acute localized vascular lesion.

I wish to ask Drs. Davison and Goodhart whether a detailed study of their case did not reveal any accessory conditions in addition to the localized area of softening. Judging from the lantern slides, the latter must have been excessive. What approximately were the dimensions of the area of softening?

DR. CHARLES DAVISON, New York: It is true, as Dr. Weil states, that lesions of the striatum do not solve the problem of the involuntary movements. I hope I did not give the impression that they did, because it is well known that involuntary movements may occur as a result of lesions elsewhere in the central nervous system. It is, however, well established that lesions of the striatum do cause involuntary movements, such as dystonic or choreiform movements, and at present I think that not only we but others have shown this to be true.

I must correct Dr. Weil in reference to the extent of the lesion in the putamen and caudate. We measured accurately the entire length of the putamen and the caudate in the anteroposterior diameter in this case. The caudate was involved for a distance of 21 mm., and the putamen, 20 mm.; only the superior surface of the two structures was affected. Their entire extent in the anteroposterior diameter in coronal sections was 5.8 cm. for the caudate and 4.7 cm. for the putamen, which is much less than one-half the size of the structures.

Many times so-called hemiballismus has been confused with hemichorea. With hemiballismus the movements are more massive and more violent and involve all the muscles of one extremity or one half of the body; the arc they describe is great. With chorea this does not always hold true unless the corpus Luysii is also involved. A number of our patients with chorea with massive movement showed involvement of the corpus Luysii; in those without massive movements the lesion was limited to the striatum.

SPECIAL ARTICLES

PHYSIOLOGIC REGULATION OF THE CEREBRAL CIRCULATION

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Until recently, diverse opinions were held concerning the factors that control the blood supply of the brain. Experimental findings of one observer were inconsistent with those of another, and clinical observations could be explained by neither. Textbooks of physiology still reflect this unsatisfactory state of affairs. During the past five years, however, investigators in a dozen laboratories have obtained results which for the first time agree on major points. A review of most of this work, together with some of the original articles, may be found in the volume entitled "The Circulation of the Brain and Spinal Cord," published by the Association for Research in Nervous and Mental Disease.[1] To this may be added several references.[2] It seems worth while to piece together the recent findings and to examine the resulting pattern. Any such attempt at synthesis unavoidably reflects the author's personal views.

From the Department of Neuropathology, the Harvard Medical School.

1. The Circulation of the Brain and Spinal Cord, Proceedings of the Association for Research in Nervous and Mental Diseases, Baltimore, Williams & Wilkins Company, 1938, vol. 18.

2. (*a*) Villaret, M.; Justin-Besançon, L.; de Sèze, S., and Cachera, R.: Physiologie de la vaso-motricité cérébrale, Rev. neurol. **65**:1174 (June) 1936. (*b*) Serota, H. M., and Gerard, R. W.: Localized Thermal Changes in the Cat's Brain, J. Neurophysiol. **1**:115 (March) 1938. (*c*) Loman, J.: Human Craniovertebral Dynamics, Am. J. Surg. **39**:479 (March) 1938. (*d*) Schneider, D.: Die Vasomotorik der Gehirndurchblutung, Zentralbl. f. Neurochir. **3**:127 (April) 1938. (*e*) Koopmans, S.: The Function of the Blood Vessels in the Brain: Effect of Sympathetic and Vagal Fibers of the Neck, Arch. néerl. de physiol. **23**:256, 1938. (*f*) Norcross, N. C.: Intracerebral Blood Flow, Arch. Neurol. & Psychiat. **40**:291 (Aug.) 1938. (*g*) Fog, M.: The Relationship Between the Blood Pressure and the Tonic Regulation of the Pial Arteries, J. Neurol. & Psychiat. **1**:187, 1938. (*h*) Forbes, H. S.; Schmidt, C. F., and Nason, G. I.: Evidence of Vasodilator Innervation in the Parietal Cortex of the Cat, Am. J. Physiol. **125**:216 (Feb.) 1939. (*i*) Penfield, W.; von Sántha, K., and Cipriani, A.: Cerebral Blood Flow During Induced Epileptiform Seizures in Animals and Man, J. Neurophysiol. **11**:257 (July) 1939. (*j*) Williams, D., and Lennox, W. G.: The Cerebral Blood-Flow in Arterial Hypertension, Arteriosclerosis, and High Intracranial Pressure, Quart. J Med. **8**:185 (July) 1939.

After review of the evidence, it is possible to make two general statements: 1. The volume of blood flow through the brain is regulated chiefly by the systemic arterial pressure. 2. This arterial pressure is not the sole regulator. Other factors play important, if subordinate, roles, some affecting the flow through the whole brain and others through only a limited region.

The accompanying table shows the chief factors which influence cerebral blood flow under physiologic conditions. The subsequent outline gives an idea of the relative importance of these factors and some of the underlying conditions. Although most of the observations have been made on animals, those of Loman and Myerson,[3] of Lennox, Gibbs and Gibbs,[4] and of Penfield and his colleagues [21] were made on nonanesthetized human subjects.

Just how far conclusions based on the animal experiments may be applied to man is difficult to determine. Many of the physiologic mechanisms found in the cat, dog and monkey are similar to those in man; others—e. g., the adjustment of cerebrospinal fluid pressure to changes in posture—are different.[5] Important structural features also, such as the bony tentorium and the exceeedingly small internal carotid artery in the cat and dog, may cause dynamic changes not found in man.

Referring to a particular condition, the circulatory response to convulsions, Penfield said: [21]

> The similarity in reaction between the unanesthetized human cortex and that of animals under Dial indicates that the Dial did not essentially alter the reactions in the animal experiments and it further suggests that conclusions drawn from experimental evidence may be applied to clinical epileptic seizures.

It is probable that much of the experimental evidence dealt with in the present paper will be found applicable to man. The effects of drugs are perhaps least likely to be similar, because there is always the complication of a previous drug—the anesthetic—in experiments on animals. It would seem wise that each conclusion drawn from animals should, whenever possible, be tested by observation on man.

FACTORS REGULATING CEREBRAL BLOOD FLOW

Extracerebral Factors.—A. The systemic arterial pressure is more important in its effect on the total cerebral blood flow than any of the

3. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Cranio-Vertebral Cavity, Am. J. Psychiat. **92**:791 (Jan.) 1936.

4. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, J. Neurol. & Psychiat. **1**:211, 1938.

5. von Storch, T. J. C.; Carmichael, E. A., and Banks, T. E.: Factors Producing Lumbar Cerebrospinal Fluid Pressure in Man in the Erect Posture, Arch. Neurol. & Psychiat. **38**:1158 (Dec.) 1937. Loman and Myerson.[3]

other factors (intracerebral or extracerebral). The arterial pressure is controlled partly from within the brain by reflexes involving the cardiovascular centers. It has been classed as extracerebral because all the effectors for those pressor or depressor reflexes (as well as for similar reflexes arising in the carotid sinus and the aortic area) lie in the arterioles of the viscera, muscles and skin, i. e., outside the brain.[6] The systemic arterial pressure is determined, furthermore, by the amount and quality of the blood returned to the heart and by the state of the heart itself. It is hardly necessary to mention that the complicated vasosensory and vasomotor mechanisms are of prime importance in maintaining an adequate and steady flow of blood to the brain.[7]

Systemic arterial pressure is related to cerebral blood flow in the following ways: A large rise in pressure causes an increase in flow and a large fall, a

Principal Factors Regulating the Normal Blood Flow of the Brain

Extracerebral Factors *
- *A.* Systemic arterial pressure
- *B.* Venous pressure
  - (*a*) In dural venous sinuses
  - (*b*) In jugular and vertebral veins

Cerebral Factors
- *A.* Changes in caliber of cerebral arteries and arterioles
  - (*a*) Active
  - (*b*) Passive
- *B.* Changes in resistance to flow in cerebral capillaries or venules

* For the sake of precision, the terms "extracerebral" and "cerebral," instead of "extracranial" and "intracranial," are used in this schema. The arteries of the dura mater, though within the skull, are branches of the external carotid artery, and are classed here as extracerebral, together with all the arteries outside the skull. The dural arteries do not react like cerebral vessels. They possess a much stronger vasoconstrictor innervation; they are not sensitive to increased tension of carbon dioxide in the blood, and they do not dilate in response to stimulation of the facial nerve or to a critical fall of blood pressure.

decrease; yet a decrease *may* occur during a slight rise in pressure or an increase during a slight fall, if an "active" change takes place in the caliber of the artery. "Active" changes will be discussed later. It is important to understand that they modify, but do not overcome, the effect on cerebral blood flow of large fluctuations in arterial pressure.

When the blood pressure starts to rise after a fall, the flow increases even above the previous rate. If the rise in pressure is abrupt the brain will be flushed with arterial blood coming through the capillaries so fast that only a small percentage of oxygen is removed. The venules draining the cerebral cortex now show a striking change in color from purple to

6. Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, Lea & Febiger, 1939, p. 562.

7. Heymans, C.: Sur les relations fonctionnelles entre le métabolisme, la respiration et la circulation, Bruxelles-méd. **38**:7 (July 19) 1936.

bright scarlet. The conditions which bring about this reaction will be discussed later.[8]

B. The venous pressure (in the large veins immediately outside the brain) seems to have little effect on the cerebral blood flow. The extracerebral veins may be divided into two groups according to their relation to the skull. 1. Dural sinuses. These vessels are so well protected that they can hardly be obstructed except by some pathologic event, such as thrombosis, tumor formation or trauma. When the lateral sinuses are obstructed bilaterally in acute experiments on dogs, compensation begins almost immediately and is well advanced in two hours.[9] In man one lateral sinus is frequently obstructed during operation without symptoms or signs of retarded circulation or of increased intracranial pressure. Occasionally, it is true, serious and even fatal results may follow unilateral obstruction, especially on the right side. The right lateral sinus usually is much larger than the left, and sometimes the latter is entirely absent. If both lateral sinuses are completely obstructed, serious symptoms develop. Under favorable circumstances these may be relieved by the removal of cerebrospinal fluid and by other measures, but it may take months for collateral circulation to become well established.[10] 2. Jugular and vertebral veins. Transient increase in pressure in these veins may occur in any of the following conditions: increase in intrathoracic or abdominal pressure, external compression of the jugular veins in the neck or change in posture (head down). Under ordinary physiologic conditions (except for transient changes) the cerebral blood flow is not signicantly retarded by these procedures.[11] This is partly due to venous anastomoses and partly to a compensatory rise in arterial pressure. These two factors counterbalance the effect of partial venous obstruction and thus maintain a steady blood flow through the brain.

It is remarkable that in patients suffering from serious obstruction to the superior vena cava, studied by Ferris,[12] cerebral symptoms were absent and the total blood flow of the brain was normal, although there was noticeable venous stasis of the face and arms. This careful work included study of the arterial blood, the internal jugular venous blood and the venous pressure.

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8. Sometimes, under abnormal conditions, one may see two venules—one purple, the other scarlet—draining adjacent cortical areas. When these venules unite, the blood in the common vessel, owing to the streamline flow, presents a longitudinally striped appearance—purple and red. Penfield has noticed the same appearance in the pial venules of epileptic patients during operation. It is seen near the epileptogenic focus, usually just after a convulsion.[1]

9. Bedford, T. H. B.: The Effect of Increased Intracranial Venous Pressure on the Pressure of the Cerebrospinal Fluid, Brain **58**:427, 1935.

10. Lurie, M. H.: Personal communication to the author.

11. Gibbs, F. A.: Personal communication to the author.

12. Ferris, E. B., Jr.: The Effect of High Intracranial Venous Pressure upon the Cerebral Circulation and Its Relation to Cerebral Symptoms, J. Clin. Investigation **18**:19 (Jan.) 1939.

Experiments on animals have shown that sudden complete closure of the superior vena cava causes only slight retardation of blood flow in the pial venules and no cyanosis or change in caliber of the arteries, veins or capillaries of the pia.

Cerebral Factors (in order of importance).—*A.* Changes in caliber of cerebral arteries or arterioles [13] occur under a variety of circumstances. If other conditions remain constant, the volume of flow through these vessels will vary directly with the change in diameter. Two sorts of changes in caliber may be recognized: active and passive, depending on the presence or absence of changes in tonus of the arterial walls.[14]

1. Active changes. Such changes in caliber have been observed under the following conditions: (*a*) Entrance of chemical substances into the arterial blood. These may gain access by absorption (hormones and gases) or by injection (drugs). Almost all the substances that have been studied cause dilation (decrease in tonus). This tends to increase the cerebral blood flow, but the actual change in flow depends on the behavior of the blood pressure.

Among the vasodilator substances, carbon dioxide is of the greatest importance. It causes a large increase in volume flow, since it not only dilates the cerebral vessels but constricts reflexly the peripheral vessels and raises the blood pressure. The blood vessels of the brain are peculiarly sensitive to slight variations in tension of carbon dioxide.[15] Epinephrine (in spite of mild constrictor action when applied locally) causes, by intravascular injection, transient dilation and increase in flow.[16] The

13. For the most part, pial arteries of from 80 to 300 microns in diameter and arterioles of from 12 to 40 microns have been studied.

14. Trauma to vessel walls causes the greatest changes in tonus. Under experimental conditions true spasm of pial arteries is seen only after strong mechanical or electrical stimuli applied directly to the vessels. Since the condition is pathologic rather than physiologic, it is not included in this classification. Villaret and Cachera (Les embolies cérébrales, Paris, Masson & Cie, 1939), studying experimental emboli (powdered glass), reported that weeks after embolism was produced the pial arterioles showed abnormal irritability. It seems possible, however, that the foreign particles were still present and were still causing mechanical irritation.

15. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Psychiat. **3**:557 (April) 1935. Lennox, Gibbs and Gibbs.[4]

16. (*a*) Forbes, H. S.; Finley, K. H., and Nason, G. I.: Cerebral Circulation: XXIV. Action of Epinephrine on Pial Vessels, Arch. Neurol. & Psychiat. **30**:957 (Nov.) 1933. (*b*) Schmidt, C. F., and Hendrix, J. P.: Action of Chemical Substances on Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:229, 1938. (*c*) Bouckaert, J. J., and Jourdan, F.: Recherches sur la physiologie et la pharmacodynamie des vaisseaux cérébraux: IV. Influence de l'adrénaline, Arch. internat. de pharmacodyn. et de thérap. **54**:109 (Aug.) 1936. (*d*) Fog, M.: Cerebral Circulation: I. Reaction of Pial Arteries to Epinephrine by Direct Application and by Intravenous Injection, Arch. Neurol. & Psychiat. **41**:109 (Jan.) 1939. (*e*) Norcross.[2f]

dilation in this case appears to be merely passive, for if the abrupt rise in blood pressure is prevented no dilation occurs.

Other vasodilator substances for which the evidence seems reliable are: acetylcholine, alcohol,[17] ether, histamine, metrazol,[18] nitrites, carbon monoxide and hydrogen sulfide.[19] Any of these substances may cause a large fall in blood pressure. When this occurs, the cerebral blood flow will decrease during the fall and increase during recovery. If the blood pressure falls only moderately with these vasodilator drugs—or if it is unchanged or rises—the flow will increase. Any of the dilator substances, therefore, will increase the flow except during an abrupt fall in arterial pressure or during the maintenance of very low pressure. The action of alcohol, for example, like that of the other drugs, varies with the dose and method of administration. By intravenous injection, in barbiturized animals, alcohol usually causes a rapid fall in blood pressure, dilation of the pial arteries and a decrease in flow, followed immediately by a large increase. (Administration of alcohol by mouth to a nonanesthetized animal caused slower and more prolonged dilation.[17]) The nitrites act somewhat like alcohol, but the depression of blood pressure is greater. The effects of both drugs are transient, but with alcohol given by mouth the dilation may last nearly an hour. Papaverine also has a vasodilator action.[20]

In contrast to the many substances which produce vasodilation, only a few have been found to cause vasoconstriction in the brain. Barium chloride and a few alkaline solutions, in suitable concentrations, are perhaps the only ones for which the evidence is satisfactory.[20] Oxygen seems to have a slight constrictor effect, and hyperpnea, with blowing off of carbon dioxide, acts similarly.[21]

In man caffeine causes a slight decrease in cerebral blood flow, in spite of a rise in blood pressure. The cerebral vasoconstriction thus indicated may be due to hyperpnea.[22] In barbiturized animals caffeine

17. Thomas, C. B.: Cerebral Circulation: XXXI. Effect of Alcohol on Cerebral Vessels, Arch. Neurol. & Psychiat. **38**:321 (Aug.) 1937.

18. Forbes, H. S., and Nason, G. I.: Unpublished results.

19. (*a*) Forbes, H. S., and Cobb, S.: Vasomotor Control of Cerebral Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:201, 1938. (*b*) Schmidt and Hendrix.[16b]

20. Bouckaert, J. J., and Jourdan, F.: Recherches sur la physiologie et la pharmacodynamie des vaisseaux cérébraux: VI. Réactions pharmacologiques des vaisseaux cérébraux, Arch. internat. de pharmacodyn. et de thérap. **54**:168 (Sept.) 1936. Personal observation.

21. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

22. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow in Man as Influenced by Adrenalin, Caffein, Amyl Nitrite and Histamine, Am. Heart J. **10**:916 (Oct.) 1935.

usually causes a fall in blood pressure, dilation of the pial arteries and (undoubtedly) a transient decrease in flow followed by an increase.[23] The evidence for solution of posterior pituitary U. S. P. is still conflicting. Ergotamine tartrate constricts arteries of the dura, but not those of the brain.[24]

This is particularly interesting because, in treatment of migraine, ergotamine tartrate was first given on the false assumption that it would relax cerebral vasospasm, which was supposed to cause the headache. Recently it has been shown that the headache is caused not by constriction of the cerebral arteries but by dilation and increased pulsation of the temporal and of the dural arteries.[25]

(*b*) Pronounced change in blood pressure. A fall in pressure is accompanied by dilation and a rise by constriction (or return to the normal caliber) of the cerebral arteries. Such a sequence is not invariable, it is true, for an abrupt change in pressure may cause a passive change in size of the arteries. This is discussed in section 2, on "Passive Changes." Fog has stressed the fact that mere resistance to passive stretching, i. e., maintenance of caliber in the face of a large rise in pressure, is also proof of an active change in tonus of the arterial walls.[26]

This active response on the part of the arteries to a change in intravascular pressure has a steadying effect on the cerebral blood flow, tending to reduce extreme fluctuations which otherwise would mirror sharp ups and downs of pressure. As a matter of fact, the crucial factor in this reaction is not the height of the blood pressure but the velocity of the blood flow through the arteries in question. This is demonstrated by the following experimental observation: When the cerebrospinal fluid pressure was raised to about 1,000 mm. of water, the pial circulation was visibly slowed and the pial arteries dilated, although the arterial pressure remained normal.[26] Ordinarily, however, the rate of flow varies directly with the arterial pressure, and the arterial caliber varies inversely both with changes in flow and with changes in pressure.

The salient feature of this inverse relation between caliber and pressure is the sudden large arterial dilation which occurs when the systemic

23. Finesinger, J. E.: Cerebral Circulation: XVIII. Effect of Caffeine on Cerebral Vessels, Arch. Neurol. & Psychiat. **28**:1290 (Dec.) 1932.

24. Pool, J. L., and Nason, G. I.: Cerebral Circulation: XXXV. The Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura and Skin of Cats, Arch. Neurol. & Psychiat. **33**:276 (Feb.) 1935.

25. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:638, 1938.

26. Wolff, H. G., and Forbes, H. S.: Cerebral Circulation: V. Observations of the Pial Circulation During Changes in Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928

arterial pressure falls to a critical level.[27] The "critical level" is relatively constant in each animal, and is usually about 70 to 80 mm. of mercury (systolic). At arterial pressures well above the "critical level" slight changes in caliber of the pial arterioles often occur, but these are not constant.

When the blood pressure, falling very slowly, reaches a point just above the "critical level," the pial arteries often show striking rhythmic dilations every half-minute or so, with rapid constrictions (or recessions) between.

The seeming paradox—fall in blood pressure plus arterial dilation plus diminished flow—is one of the most unequivocal and easily demonstrated of phenomena. Its demonstration illustrates the advantage of actual inspection of blood vessels in the living subject. Even the keenest observers, using indirect methods of study, have failed to detect this physiologic mechanism.

Although there is no doubt as to the existence of the arterial dilation, the primary cause is not certain. It seems probable that it is chemical (asphyxial) rather than reflex.[28] There is difference of opinion, also, as to the relative importance of this type of regulation. Fog expressed the belief that it plays an important role in controlling the circulation of the brain—ironing out excessive fluctuations, which occur even under normal conditions.[2g] I am inclined to believe that it acts chiefly as an emergency measure when conditions become critical.

(*c*) Local activity of neurons. When the retina, for example, is stimulated by light, both the lateral geniculate body and the visual cortex show signs of increased blood flow. Under these circumstances the effect is local (or regional). The evidence for increased flow and arteriolar dilation has been obtained chiefly by thermoelectric methods. The results have been confirmed by three investigators.[29] This regional vasodilation and increase in blood flow are probably caused by the increased metabolism of the active nerve elements, with a corresponding rise in carbon dioxide tension.[29a] The total blood flow of the brain is little affected; yet the local needs are cared for.

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27. Forbes, H. S.; Nason, G. I., and Wortman, R. C.: Cerebral Circulation: XLIV. Vasodilation in the Pia Following Stimulation of the Vagus, Aortic and Carotid Sinus Nerves, Arch. Neurol. & Psychiat. **37**:334 (Feb.) 1937.

28. Forbes and Cobb.[19a] Irving described a somewhat similar vascular reaction in diving animals. He expressed the opinion that this may be regulated by nerve reflexes, but his evidence for the latter is not entirely convincing (Am. J. Physiol. **122**:207 [April] 1938).

29. (*a*) Gerard, R. W.: Brain Metabolism and Circulation, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:316, 1938. (*b*) von Sántha, K., and Cipriani, A.: Focal Alterations in Subcortical Circulation Resulting from Stimulation of Cerebral Cortex: Experimental Demonstration of Cortico-Subcortical Connections, ibid. **18**:346, 1938. (*c*) Schmidt and Hendrix.[16b]

(*d*) Activity of the cerebral vasodilator nerves in animals, resulting in dilation of the pial arteries, together with increased blood flow in the parietal cortex.[2h] Parasympathetic fibers of the seventh cranial nerve (and the geniculate ganglion) are the only nerves which have been found to cause active dilation of cerebral vessels. This was first demonstrated by Penfield in 1931.[30] The vagus, aortic and carotid sinus nerves have no such effect.[27]

(*e*) Activity of cerebral vasoconstrictor nerves in animals, resulting in weak constriction of the pial arteries and venules, accompanied by diminished blood flow in the pia, cortex and basal ganglia.[31] Sympathetic fibers from the stellate ganglion and cervical portion of the sympathetic trunk are responsible for this mild constrictor effect. In the cat it has been found that these fibers accompany the internal carotid artery and constitute a part of the lowest group of fibers as these fan out and pass below the cochlea.[32] In man there is as yet no positive evidence of vasomotor nerves in the brain, though Chorobski and Penfield traced sympathetic fibers from the superior cervical ganglion to the wall of the internal carotid artery, where subsidiary ganglia were seen.[30] It is probable that a weakly acting apparatus, similar to that of the monkey, will be found.

2. Passive changes. Such changes in caliber of the cerebral arteries occur during an abrupt rise or fall in arterial pressure. These changes are not important unless they are superimposed on changes in tonus of the arterial walls. For example, a sudden rise in blood pressure will cause little, if any, change in caliber in a normal artery, but if the artery is relaxed (by asphyxia or by a critically low blood pressure) it will become still further dilated "passively" when the blood pressure starts to rise abruptly. The maximal dilation thus caused is striking—the flow accelerates; the veins and venules become bright red, like the arteries, and the whole surface of the brain is flushed. Then, while the arterial pressure remains high and the flow rapid, the arteries—on the surface of the brain, at least—regain their tonus, constricting "actively" against the intravascular pressure, to assume their normal size.

B. Changes in resistance to flow within cerebral capillaries or venules may be caused by extreme hydration or dehydration. Measurable alterations in cerebral volume—edema or shrinkage—may occur under physiologic conditions. Edema tends to reduce the blood flow by narrowing the capillaries and venules. Loss of fluid from the perivascular spaces, on the other hand, tends to dilate the capillaries and venules. This will

30. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, Arch. Neurol. & Psychiat. **28**:1257 (Dec.) 1932.

31. Forbes and Cobb.[19a] Norcross.[2f]

32. Forbes, H. S., and Nason, G. I.: Unpublished results.

increase the amount of blood in the cerebral vessels, but will not necessarily increase the flow. In fact, when the animal is strongly dehydrated by injection of a hypertonic solution, the flow through the venules on the surface of the brain is visibly retarded.[33] But this state is abnormal and outside the physiologic range. Unless a pathologic condition is present, it is doubtful if the blood flow of the brain will be appreciably altered by changes in the water balance.

Even under pathologic conditions, such as cerebral arteriosclerosis, the total cerebral blood flow of patients has been found to be within normal limits.[21] In the presence of such obstacles the maintenance of a steady flow is remarkable.

COMMENT

It seems probable that coordination between activity and blood flow, even for small groups of nerve cells, is made possible by the local response referred to in section *c*. Such coordination would be of vital importance during intense neural activity involving limited areas of the brain, and one would expect to find such a mechanism intimately related to fatigue and to recovery. The rate of removal of waste products from cells or synapses, during excessive activity of particular regions of the cortex, may partly determine the rate of fatigue of particular functions.[34]

Campbell has found a positive correlation between oxidase content—which serves as an index of oxygen utilization, and hence of functional activity—and regional vascularity.[35] Scharrer, in an ingenious research on the opossum's brain, has just obtained additional evidence of a quantitative relationship between metabolic activity and capillary density.[36] These bits of concrete evidence, linking function and structure, are opportune and of particular interest in connection with the hypothalamus. Here, Finley has demonstrated the presence of an exceedingly dense capillary network within two nuceli—the "supra-optic" and the "paraventricular."[37] It is interesting, too, that regions rich in synapses are

33. Forbes, H. S., and Nason, G. I.: Cerebral Circulation: XLI. Vascular Responses to (*A*) Hypertonic Solutions and (*B*) Withdrawal of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **34**:533 (Sept.) 1935.

34. This does not imply that arterioles in the brain open and close during activity and rest, as they do in muscles. On the contrary, such changes have never been noted during prolonged observation of the pial vessels. Additional evidence against closure of cerebral arterioles (in the opossum) has been reported recently by Scharrer.[36]

35. Campbell, A. C. P.: Variation in Vascularity and Oxidase Content in Different Regions of the Brain of the Cat, Arch. Neurol. & Psychiat. **41**:223 (Feb.) 1939.

36. Scharrer, E.: The Functional Significance of the Capillary Bed in the Brain of the Opossum, Anat. Rec. **75**:319 (Nov. 25) 1939.

37. Finley, K. H.: The Capillary Beds of the Paraventricular and Supra-Optic Nuclei of the Hypothalamus, J. Comp. Neurol. **71**:1, 1939.

rich also in capillaries.[38] In any given region in the brain an increase in growth of capillaries probably follows repeated activity, as it does elsewhere in the body.

CONCLUSION

The main results of these physiologic controls seem to be: 1. The maintenance in the brain of a total blood flow which is steadier than that of other organs, and is better safeguarded.

2. The maintenance—within rather narrow limits—of an optimal carbon dioxide tension and hydrogen ion concentration in the immediate environment of the nerve cells of the brain.

3. The provision for local variations in flow according to changing local needs.

Dr. T. J. C. von Storch gave helpful criticism and suggestions.

38. Dunning, H. S., and Wolff, H. G.: The Relative Vascularity of Various Parts of the Central and Peripheral Nervous System of the Cat, and Its Relation to Function, J. Comp. Neurol. **67**:433, 1937.

News and Comment

BOOK FOR DISTRIBUTION

About April 1940, a volume entitled "Psychological Studies in Dementia Praecox," by Isabelle Kendig, Ph.D., and Winifred Richmond, Ph.D., will be published at Ann Arbor, Mich., by Edwards Brothers, Inc. The work has been done by the department of psychology of Saint Elizabeths Hospital, Washington, D. C., and includes the following three studies, together with extensive bibliographies: Dementia Praecox and General Intelligence; Patterns of Mental Function in Dementia Praecox; Dementia Praecox and the Concept of Deterioration.

The research on which the papers are based was financed by private grants. While the volume is given without cost to those interested, it will be necessary to send 50 cents a copy to cover the costs of mailing. Requests for copies should be sent to Dr. Isabelle Kendig, Saint Elizabeths Hospital, Washington, D. C.

AMERICAN PUBLIC HEALTH ASSOCIATION

The sixty-ninth annual meeting of the American Public Health Association will be held in Detroit, Oct. 8 to 11, 1940, at the Book-Cadillac Hotel. The Michigan Public Health Association, the American School Health Association, the International Society of Medical Health Officers, the Association of Women in Public Health and a number of other allied and related organizations will meet in conjunction with the association. The Michigan Committee on Arrangements is headed by Mr. Abner Larned, of Detroit. Dr. Henry F. Vaughan, health commissioner of Detroit, is executive secretary.

A health exhibit will be held in connection with the meeting, and an institute on health education is scheduled prior to the official opening. Dr. Reginald M. Atwater is executive secretary of the American Public Health Association, with offices at 50 West Fiftieth Street, New York.

Abstracts from Current Literature

Anatomy and Embryology

THE PITUITARY GLAND OF THE ATLANTIC SALMON. ALICE S. WOODMAN, J. Morphol. **65**:411 (Nov.) 1939.

The pituitary gland of the Atlantic salmon originates as a solid mass of ectodermal epithelium ten or eleven weeks after fertilization of the egg. Soon after hatching, at about 25 weeks, the brain contribution is evident. Morphologic and histologic differentiation proceeds through a series of changes for several years, but does not become complete until the salmon has spent some time in the sea. The principal lobe consists of discrete follicles with definite lumens lined with intensely eosinophilic columnar epithelium, which appears homogeneous. Once established, these follicles retain the same characteristics throughout the life of the fish, except for possible increase in size. This division forms from one-sixth to one-fourth the volume of the organ. This follicular principal lobe places the pituitary gland of the Atlantic salmon among the more primitive teleostean types.

The transitional part has both eosinophilic and basophilic cells—the latter, with varying degrees of staining reaction, generally predominating. No typical chromophobic cells are present. This part contributes cells or follicles to the two adjoining epithelial divisions of the gland.

The pars intermedia and the pars nervosa form an intimate anatomic association. The former contains basophilic cells, which predominate, and a varying number of eosinophilic cells. If the close association of these cells with the blood vessels on the surface of the pars nervosa is taken into consideration, it would seem that here is a place where transfer of secretion from the pars intermedia may be made directly into the blood stream.

Correlation between sexual activity and definitive adult differentiation is not morphologically evident. Sexual activity may occur early in the life of the male salmon, before complete differentiation of the pituitary gland has been accomplished. The cytoplasm of the secreting cells of this gland does not exhibit granules as indication of the state of secretory activity, but has a homogeneous appearance suggestive of a "colloid" content.

WYMAN, Boston.

Physiology and Biochemistry

ESTRIN (ESTROGEN) EXCRETION IN PSYCHOTIC PATIENTS. JOHN LANSBURY and JOSEPH HUGHES, Am. J. Psychiat. **95**:1119, 1939.

Lansbury and Hughes point out that almost uniformly it has been reported that estrogen in the blood and urine of female schizophrenic patients is either diminished or absent. They report the estrogen curves during a full intermenstrual period for each of 7 patients—5 with schizophrenia, 1 with manic-depressive psychosis, depressed type, and 1 with an unclassified psychosis. The average daily output of estrogen was normal for 5 patients. The estrogen curves for these patients fell within normal limits, as did also the total monthly output.

FORSTER, Boston.

CHEMICAL MEDIATION IN CRUSTACEANS: III. ACETYLCHOLINE AND AUTOTOMY IN PETROLISTHES ARMATUS (GIBBES). J. H. WELSH and H. H. HASKIN, Biol. Bull. **76**:405 (June) 1939.

Acetylcholine normally plays a role in the autotomy reflex (the dropping off of a leg) of the crustacean Petrolisthes, probably by acting as a mediator of impulses between the motor nerve and the autotomizer muscle of a leg.

COBB, Boston.

A STUDY OF THE SPLEEN IN A CASE OF NIEMANN-PICK DISEASE. ERWIN CHARGAFF, J. Biol. Chem. **130**:503, 1939.

Chargaff has confirmed Klenk's finding that sphingomyelin accumulates in large amounts in the spleen of patients with Niemann-Pick disease. The monoaminophosphatides present consisted chiefly of cephalin. It will be recalled that the brain is involved in Niemann-Pick disease much as is the spleen.

PAGE, Indianapolis.

EFFECT OF CONTINUOUS LIGHT ON PERIODIC SPONTANEOUS ACTIVITY OF WHITE-FOOTED MICE (PEROMYSCUS). MAYNARD S. JOHNSON, J. Exper. Zoöl. **82**:315 (Nov.) 1939.

Adult male white-footed mice, Peromyscus leucopus noveboracensis, were used. They were caught, uninjured, in live traps in suburban woods. Kymographic records of the activity of a single mouse were made by means of a marker attached to a cage and moving as the cage moved. In continuous light the daily activity rhythm of Peromyscus persists, but is modified, the time of the daily period of activity being progressively later on successive days. The rate of shift in time of the daily activity period remains constant with constant light intensity, but changes with change in light intensity. When logarithms of rate and intensity are plotted, the points are arranged along straight lines. Continuous light shortens and interrupts the daily period of activity, and at the higher intensities used makes the active period scarcely distinguishable from the inactive phase of the daily cycle. Apparently, light has an inhibiting action on activity. A well defined rhythm of activity persists after eighteen months in the absence of any exposure to daylight or daily change in light and dark.

WYMAN, Boston.

THE METRAZOL SEIZURE AND ITS SIGNIFICANCE FOR THE PATHOPHYSIOLOGY OF THE EPILEPTIC ATTACK. HANS STRAUSS, CARNEY LANDIS and WILLIAM A. HUNT, J. Nerv. & Ment. Dis. **90**:439 (Oct.) 1939.

Strauss, Landis and Hunt studied the convulsions produced by metrazol with ultrarapid moving pictures and simultaneous electromyograms from various antagonistic muscle groups. They found that the completely developed seizure lasted from forty-five to seventy seconds and could be divided into three main stages. The first clonic stage marked the beginning of the convulsion and was characterized by two to four double movements per second, made up of phases of adduction and abduction. The first phase consisted of adduction and inward rotation of all four extremities, with forward elevation of the shoulders and flexion of the elbows, hips, knees, neck and trunk. The face was usually pale, and the eyes and mouth were open. The second phase consisted of abduction of all extremities, with flexion of the elbows, hips and knees, pronation of the arms and slight outward rotation of the lower extremities and extension of the neck and trunk. The tonic stage followed, consisting essentially of decerebrate rigidity, with cyanosis, closed eyes, open mouth, distorted features, hyperextension of the neck and trunk and adduction, inward rotation and extension of all four extremities, except for slight flexion of the hips. During this stage the electromyogram showed continuous high potentials in all muscles, with a frequency of 20 impulses

per second. The second clonic stage, which marked the end of the seizure, was characterized by alternating contraction and relaxation—a repeated interruption of the preceding tonic contractions. The result was alternating extension and flexion of the trunk, with various movements of the extremities representing intermittent innervations, separated by relaxations in which the action of gravity was manifested.

From these observations, Strauss, Landis and Hunt conclude that the first and the second clonic stage have quite different central mechanisms. They believe that the first is the expression of cortical stimulation, with reciprocal innervation preserved, while the second, like the preceding tonic stage, is the result of the release of nuclei in the medulla oblongata. They suggest that the tonic and the clonic stages of the metrazol seizure correspond closely to those of the epileptic convulsion.

MACKAY, Chicago.

Neuropathology

FATAL COMPLICATION FOLLOWING METRAZOL TREATMENTS FOR SCHIZOPHRENIA. J. PESSIN and H. REESE, Am. J. Psychiat. **96**:393, 1939.

Pessin and Reese report the case of a man aged 24 who had always been seclusive and who was found to have paranoid delusions. He was given 5 cc. of a 10 per cent solution of metrazol intravenously, with a resultant convulsion lasting fifty-five seconds, followed by fatal respiratory failure. Autopsy showed acute cardiac dilatation with visceral congestion; cerebral edema with a pressure cone; swelling and shrinkage of nerve cells, especially in the corpus striatum, the thalamus and the cerebellum; swelling of cells in the vagal and hypoglossal nuclei, and minute perivascular hemorrhages, especially in the medial part of the thalamus. Pessin and Reese believe that a lumbar puncture performed forty-eight hours before the injection may have contributed to the effect and suggest a longer period between the puncture and administration of metrazol.

FORSTER, Boston.

CENTRAL NERVOUS SYSTEM CHANGES PRODUCED BY INSULIN. K. E. APPEL, B. J. ALPERS, D. W. HASTINGS and JOSEPH HUGHES, Am. J. Psychiat. **96**: 397, 1939.

Appel, Alpers, Hastings and Hughes studied the changes in the central nervous system produced by insulin in 9 cats. Eight of the cats were given an average dose of 6 units of insulin a day for from nine to twenty-eight days, with one or more convulsions per day. One cat received one injection of 60 units. All the animals were killed. Of the group of 8 cats, 2 showed no changes on microscopic examination; 2 showed mild ischemia of the ganglion cells, evidenced by paler staining in 1 case and by shrunken, pyknotic changes in scattered cells in the other, and 5 showed ischemic changes in scattered cells, especially in the frontal areas, regardless of the cell layer. The Purkinje cells of the cerebellum seemed more involved. In the cat which received 60 units the cortical cells of the frontal area showed widespread involvement and the Purkinje cells were affected. The authors agree that a possible explanation for the ischemic changes is the inability of the brain to carry out its oxidative processes because of the action of insulin.

FORSTER, Boston.

ACTION OF BEE'S VENOM ON THE CENTRAL NERVOUS SYSTEM AND THE PERIPHERAL NERVES. L. CORNIL, J. E. PAILLAS and J. CHOUQUET, Ann. d'anat. path. **16**:908 (July) 1939.

Mice and guinea pigs survived subcutaneous injection of sublethal doses of bee's venom for several days. The brains of the experimental animals were markedly congested. There was generalized disease of ganglion cells, with disso-

lution of Nissl granules and shrinkage of the nucleus. In the white matter irregularly distributed areas of demyelination were seen. Similar areas were also found in the spinal cord and in the sciatic nerve.

WEIL, Chicago.

INFLAMMATORY SCLEROSIS OF THE WHITE MATTER OF THE HEMISPHERES. LUDO VAN BOGAERT and JACQUES DE BUSSCHER, Rev. neurol. **71**:679, 1939.

Van Bogaert and de Busscher report the case of a boy aged 8 years who had been at the head of his class and who began to fail in his schoolwork, particularly in arithmetic. His writing became disordered and incorrect. He became coarse and brutal, had noctural terrors, talked at night and seemed to have hallucinations. His writing became more and more impaired, with omission of letters or reduplication of syllables. Finally, he could not read except in a mirror. Other signs of extensive and severe visual dysgnosia developed, such as taking strangers in the street for his father, confusion of his possessions with those of his fellow pupils, searching vainly at table for familiar objects and inability to copy except by servile reproduction of the words, without comprehending them. Finally, after four months, his parents believed him to have become an idiot and took him to a physician. Examination revealed bilateral papilledema, a cracked pot sound on percussion of the skull, slight, questionable right hemiparesis and clumsy gait with occasional falling. The reflexes were all normal. In addition to visual agnosia, there were apraxia and advanced aphasia of the semantic type. There were attacks of pallor, opisthotonos and generalized rigidity, recalling Jackson's cerebellar fits. There was no evidence of syphilis or other infection. Roentgenograms of the skull showed mottling characteristic of intracranial pressure. The symptoms increased. Vomiting, headache and conjugate deviation of the head and eyes to the right appeared. A diagnosis of glioma of the left parieto-occipital region was made. Craniotomy revealed a tense and nonpulsating dura, but no tumor. Death with hyperthermia followed. There was diffuse, moderate demyelination of the cerebral and cerebellar white matter, most marked in the parieto-occipital region, accompanied by diffuse gliosis. The latter was more extensive than the loss of myelin. In the white matter of both hemispheres were multiple, focal, perivascular infiltrations with lymphocytes and plasma cells. The cortex had inflammatory nodules consisting of similar infiltrations, together with neuroglial and microglial proliferation, formation of rod cells, satellitosis and destruction of ganglion cells in layers II, III, V and VI. The overlying leptomeninx showed severe infiltration with lymphocytes and plasma cells. These lesions were particularly severe in the cunei, the precunei and the superior temporal and interparietal sulci. The central gray nuclei, the substantia nigra, the substantia reticulata of the brain stem and the nucleus of the corpus restiforme showed similar lesions. The pons showed diffuse marginal gliosis. The topographic distribution of the lesions was characteristic of diffuse sclerosis, the site of greatest intensity being in the occipital pole, lateral to the optic radiations. A peculiar feature was the intense inflammation of the gray as well as of the white matter, which could not be explained as reactive since no products of disintegration were seen in the inflamed areas. The condition is classified as inflammatory sclerosis of the white matter of Spielmeyer, and is believed to be caused by an infection of unknown nature.

LIBER, New York.

DIFFUSE DISEASE OF THE CEREBRAL HEMISPHERES FOLLOWING CARBON MONOXIDE POISONING, WITH REMISSION. HANS JACOB, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:161 (March) 1939.

Jacob reports the case of a woman aged 48 who made a suicidal attempt after a quarrel with her husband. She was found unconscious in a gas-filled apartment. She rallied after admission to the hospital and was discharged nine days later, with no evident sequelae except affective lability. She continued to be apparently well for the fortnight following her discharge and was able to return

to work. She then became careless in her work and increasingly apathetic and finally remained in bed, refusing to talk. Speech and gait became slower. She finally became confused and had to be sent back to the hospital, twenty-three days after her discharge.

Except for an indolent infiltration of the left thigh, physical examination gave negative results. She was confused, and rapport was defective. She grimaced and attitudinized. She was inaccessible and refused food. Three days after her second admission she was found to have the following symptoms: an inconstant Trömner reflex on the left side, an inconstant Oppenheim reflex bilaterally and inability to walk or stand. She appeared confused and did not answer questions. There were no spontaneous productions. She swallowed poorly and was incontinent. There were 4 cells per cubic millimeter of cisternal fluid; the sugar content of the fluid was 85 mg. per hundred cubic centimeters; the Wassermann reactions of the blood and spinal fluid were negative; the gum mastic curve was normal; an encephalogram revealed nothing abnormal. The patient died four days after her second admission and forty days after the carbon monoxide poisoning.

In addition to aspiration pneumonia, there was diffuse disease of the brain. Macroscopically, there were yellowish areas of softening in the anterior part of the corpus callosum, in the region of the internal capsules and in the white substance of the occipital lobes. There were rose-colored disease foci in other parts of the white substance of the cerebral hemispheres.

Histologically, the most prominent change was widespread demyelination, involving especially the centrum ovale. The more deeply lying white substance was not spared. The demyelination appeared diffuse, though in some areas it was spotty. The arcuate fibers were spared throughout. There was a marked glial reaction especially of gemästete forms. There was destruction of nerve fibers in the areas of demyelination. Gitter cells were rare and were found only in some foci of degeneration in the corpus callosum. There were sparse changes in the cerebral cortex; these were limited to a few areas of necrobiosis and fatty degeneration of endothelial cells. Fat was seen free in the tissues. There were mild vascular congestion, rare perivascular lymphocytic infiltrations and deposits of corpora amylacea in the molecular layer of the cerebellum and the corpus callosum.

Jacob found 6 other cases in which there was a history of remission soon after exposure but the patient died. In all these cases, the author observed diffuse demyelination similar to that in his own, with few or no areas of softening or hemorrhages. In other cases, such as those reported by Strecker, Taft and Stewart, in which there was no free clinical interval, multiple areas of softening and hemorrhage were present in the cortex and subcortex. These changes were present occasionally, in addition to the diffuse destruction of the white matter.

There was no clearcut relation of the area of demyelination to the blood vessels. This, together with the absence of gitter cells, is considered by the author as evidence for the theory that there was a direct toxic effect of the carbon monoxide on the white substance of the brain and its glial components. There are insufficient data to support the hypothesis of changes secondary to functional spasm of the blood vessels.

SAVITSKY, New York.

Psychiatry and Psychopathology

THE BIOCHEMISTRY OF MANIC-DEPRESSIVE PSYCHOSIS. R. A. MCFARLAND and H. GOLDSTEIN, Am. J. Psychiat. **96**:21, 1939.

McFarland and Goldstein review the literature concerned with the following biochemical findings in the blood of patients with manic-depressive psychoses: sugar, sugar tolerance, acidity and alkali reserve, calcium and inorganic phosphorus, nitrogenous substances, lipoids and chlorides. The most significant findings were disturbances of carbohydrate and lipoid metabolism. The manic patients showed slight increases in the level of blood sugar; the depressed patients tended

to be defective in sugar tolerance. The lipoid values were high in the manic patients; the calcium values also were slightly increased in manic states. The aberrations of sugar metabolism may well be a symptom of the illness, reflecting the abnormalities of emotional control.

FORSTER, Boston.

PSYCHOGENIC FACTORS IN ASTHMA. THOMAS M. FRENCH, Am. J. Psychiat. **96**:87, 1939.

French reviewed the records of 32 asthmatic patients who had been psychoanalyzed and found that they varied considerably in their personality traits. A common emotional factor in precipitating asthmatic attacks was a temptation which threatened to estrange the patient from a parental figure, coupled with an urge to confess to the mother and so to regain her love. The fear to make this confession evoked the asthmatic attack.

French points out the customary sexual nature of the temptation and the seductive and prohibitive role that the mother of the patient has frequently played. The role of the father is chiefly that of a mother substitute. Other threats of loss of the mother love occurred also, such as the birth of a younger child or realization of the mother's pregnancy. The usual precipitating factor was found to be sexual temptation rather than forbidden gratification, and the ensuing attack was regarded as a reaction of acute helplessness, for the conflict was too intense for the ego to master. Freedom from attacks was obtained by defense mechanisms, such as regaining sympathy and affection by confession or utilization of illness, attempting to master a traumatic event by active repetition or withdrawing from the situation of temptation and obtaining independence of the mother by means of anal or autoerotic substitutes. In some patients the sensitizing substance was found to be of psychologic importance. French states that in a number of patients attacks were greatly relieved by analysis.

FORSTER, Boston.

METRAZOL SHOCK TREATMENT. FREDRICK C. REDLICH, Am. J. Psychiat. **96**:193, 1939.

Redlich studied 13 patients treated with metrazol, with particular reference to the calcium, potassium, sodium, chloride and dextrose contents of the serum and the sedimentation rate of the blood before, during and after the convulsions. The sodium chloride content of the serum was found to be diminished after the seizure, while the dextrose levels were higher. The sedimentation rates were retarded. When metrazol was given during insulin coma, the dose of metrazol required was significantly decreased. In both animals and patients Redlich found that barbiturates and scopolamine were most effective in increasing the tolerance to metrazol, while paraldehyde and chloral hydrate were less effective. In man he found bromides of no avail. He concluded that metrazol acts on the centers of the brain stem. Sensitivity to metrazol was increased by the administration of carbon dioxide, ephedrine, epinephrine and thyroxin. Of these carbon dioxide was the most effective. Alkalinization and variations in water balance were ineffectual.

FORSTER, Boston.

THE REACTIONS AND BEHAVIOR OF SCHIZOPHRENIC PATIENTS TREATED WITH METRAZOL AND CAMPHOR. BERNARD GLUECK and NATHAN W. ACKERMAN, J. Nerv. & Ment. Dis. **90**:310 (Sept.) 1939.

Glueck and Ackerman describe the phenomena observed during the treatment of schizophrenic patients with camphor and metrazol and advance a psychologic theory to explain the phenomena. In presenting such a theory they do not deny the possible organic substrata of the disease. They describe schizophrenia as a distorted personality structure, which represents an equilibrium between ego-

destructive tensions arising in the frustration of instinct and the ego-constructive efforts of the organism. Treatment was administered in 60 cases and completed in 45. Of these, the illness in 5 was acute (of less than nine months' duration) and in 40 chronic (of from one and a half to twelve years' duration). Intramuscular injections of camphor were given only to patients who were in a hopeless, chronically vegetative state, in order to transform the stable psychotic adjustment into an acute, unstable reaction. Metrazol was then given to reduce the latter reaction to normal. In the 5 cases of the acute form and in 12 of the 40 cases of the chronic form a social remission was secured, and in 8 other cases of the chronic type there was considerable improvement. A follow-up study of from one to eighteen months revealed that relapses had occurred in 8 cases, and readmission was necessary.

Glueck and Ackerman describe four phenomonologic stages during treatment with metrazol. In the first, lasting a week or ten days, the patient is forced by the threat involved in the treatment to make an effort toward external adaptation. He reacts less acutely to hallucinations and shows active emotional attitudes toward others, apparently seeking protection from the treatments. In the second stage, lasting until from the second to the fourth week, toxic confusion appears, perhaps with reversion to deeper psychotic patterns. Fear of the treatment is great, and escape may be attempted. Hallucinations are blocked, delusional formations are ruptured, and the patient is perplexed. The third stage lasts another eight to ten weeks, with increasing evidence of toxicity, confusion and fear of treatment. However, affect becomes more appropriate, and neurotic manifestations may appear. In some patients acute psychotic episodes and deeper reversion indicate a poor prognosis. In the fourth stage treatment is terminated, toxicity and confusion lessen and the patient becomes more accessible. In unfavorable cases the original psychotic patterns reappear but in others a reality-oriented personality appears, which is characteristic of the prepsychotic personality.

Camphor administered intramuscularly produces local and referred pain, weakness, nausea, vomiting, nystagmus, vertigo, ataxia, spasms and single or multiple grand and petit mal seizures—all within three or four hours after the injection. Psychologically, there are confusion, clouding of consciousness and frequently anxious vigilance because of the threat of the treatment. Delusions become chaotic and unsystematized and the patient's speech voluble, confused or incoherent. Retarded patients may become restless and hyperactive with mounting anxiety and fear of treatment.

The phenomena observed during treatment of schizophrenic patients with camphor and metrazol are extraordinary and include rapid transformations from severe psychosis to superficial normality, from static, deteriorated schizophrenia to acute disorganization or from complete apathy to panic. Rapid establishment of transference may occur in patients formerly inaccessible. The use of camphor seems to evoke severe anxiety, even panic, with the result that the patient seeks the aid of others and establishes plastic emotional attitudes. He loses the stability and security he had achieved in his psychosis and thus gains an opportunity to resynthesize a more normal ego structure. As a rule, however, metrazol convulsive therapy must be added to produce remissions. The latter drug seems to disrupt the equilibrium which has been established between the processes of ego dissolution and ego preservation in the psychosis. So drastically is the complete destruction of the ego threatened that the opposing tendency to reconstitution of the ego is intensified. Shock therapy seems not to be specific. "The reaction of the patient's personality to the effects of treatment determines the outcome." Glueck and Ackerman propose the thesis that treatment with camphor and metrazol, by its profound threat to the patient's personality, drives it back to a primitive undifferentiated biologic level and in so doing facilitates a more normal redifferentiation.

MACKAY, Chicago.

HYSTERICAL AMNESIA RELIEVED BY INDUCED CONVULSIONS. G. S. INGALLS, J. Nerv. & Ment. Dis. **90**:453 (Oct.) 1939.

Ingalls reports the case of a woman aged 32 whose hysterical amnesia for her entire past life was not removed by treatment with sodium amytal, attempted hypnosis, suggestion and various types of association. Four injections of metrazol resulted in three convulsive seizures, after the last of which she regained, within thirty minutes, complete memory of her past.

MACKAY, Chicago.

CATATONIC SYNDROME OF ACUTE CANNABIS PSYCHOSES. P. SCOURAS, Encéphale **1**:78, 1939.

Scouras reports the case of a man aged 21 who was admitted to a hospital in Greece because he had been found walking absent-mindedly and with uncertain gait after a regiment of troops. He was in a catatonic state. He was mute, except for occasionally uttering the one word "finished." He stood in a rigid, half-flexed posture and marked time rhythmically with his feet. When undisturbed, he sat down cross legged, in oriental fashion, and went through all the motions of preparing, lighting and smoking a narghile. He reacted to slang expressions employed by drug addicts with a smile and with broken expressions of pleasure with reference to the drug. If words such as "police" or "prison" were spoken in his presence, he assumed facial expressions of fear, trembled and seemed to look for a hiding place. Examination revealed cerea flexibilitas alternating with negativism. Paradoxic and fatiguing postures were preserved for hours. The reflexes were lively. The pulse rate was 120. Blowing a whistle provoked a fear reaction. A drawing of a narghile provoked a pleasure reaction. After twelve days the patient's condition improved rapidly. He then related his history with perfect lucidity. Since the age of 13 he had smoked hashish and had had many contacts with the police following numerous brawls. While in the army, he had stabbed a policeman and was condemned to ten months' imprisonment, during which he had suffered a similar catatonic syndrome. Scouras has observed 1 other case of acute catatonia in a hashish addict. Catatonia usually occurs in old addicts, who use large doses. It is explained by the release of automatic subcortical mechanisms, which function outside the domain of consciousness.

LIBER, New York.

ANOREXIA NERVOSA AND ITS IMMEDIATE THERAPY. P. CHATAGNON and P. SCHERRER, Presse méd. **47**:1277 (Aug. 23) 1939.

Chatagnon and Scherrer discuss the symptomatology and therapy of anorexia nervosa. Persons affected are generally females between the ages of 15 and 25 years. The clinical picture presents the following features: gradual self restriction of food leading to extreme emaciation, with a possible decline in weight from 132 to 55 pounds (60 to 25 Kg.); excessive physical and mental activity, in striking contrast to the physical deterioration; growth of bizarre, one-sided gastronomic tastes, e. g., a desire for prunes, biscuits, olives or unseasoned salads, and complete apathy in the face of bodily degeneration. Food forcibly administered is rejected by self-induced exertions. Amenorrhea is present. Usually there are found a neuropathic heredity and an unfavorable family environment provoking, on occasion, an inferiority complex toward a successful member of the family of the same sex. In certain cases the psychosis may be prodromal to dementia praecox; the majority of the patients show conditions bordering on obsession. A fatal outcome is exceptional; however, some investigators set the mortality rate at 13 per hundred. Relapse after recovery is always possible. The authors discuss and reject the various nosologic classifications of anorexia nervosa within the framework of an established neurosis; neither do they favor an endocrine origin of the disease, in spite of parallel indications simulating anorexia nervosa. They differentiate particularly between anorexia nervosa and Simmonds' syndrome. In

Simmonds' syndrome emaciation develops gradually without an appreciable diminution in food intake or, in its incipience, with none at all; there is present only simple loss of appetite or distaste for certain foods, which the patient may seek to overcome and for which the metabolic dysfunction of his organism penalizes him by diarrhea; mental disorders are late, and are characterized by melancholia and unaccompanied with physical self neglect. On the other hand, in anorexia nervosa emaciation is the direct result of a refusal of food that excludes all cooperation of the patient to improve his condition, the patient not only forcibly resisting alimentation but deliberately regurgitating what he has consumed; mental disturbances are immediate and compatible with a high degree of alert activity. Even amenorrhea is secondary in anorexia nervosa. According to the authors, therapy consists in isolating the patient in a sanatorium or hospital, in artificial alimentation and in psychotherapy, with the exclusion of medicaments of all kinds. Therapy will vary according to whether the patient is in an advanced or an incipient stage of the disease. Artificial alimentation in both classes of patients consists, with due regard to the age of the patient, of two daily doses preferably of raw sweet milk with the addition of the yolks of one or two fresh raw eggs, together with fresh fruit juices (lemon, orange and the like). To restore tissue balance, from 250 to 500 cc. of a solution of dextrose is daily administered subcutaneously for a variable period, and occasionally physiologic solution of sodium chloride is given by injection. Reeducation of the patient in the use of his muscles is also necessary. In cases in which the patient is presented at once for clinical study, psychotherapy should be employed immediately and should enlist also the cooperation of the family physician. Readjustment of the patient to social and family environment after release from the institution constitutes a problem.

J. A. M. A.

Diseases of the Brain

CONSTITUTIONAL DIFFERENCES BETWEEN DETERIORATED AND NON-DETERIORATED PATIENTS WITH EPILEPSY. HARRY A. PASKIND and MEYER BROWN, Am. J. Psychiat. **95**:901, 1939.

Paskind and Brown studied 50 patients with deterioration and 39 patients with no deterioration, using the same age, race and sex groups and the technics of Martin, Saller and Draper. They recorded 80 measurements and computed 57 indexes. For the most part, they found the mean measurements to be greater for the deteriorated patients. Consistent differences occurred between the indexes for weight and height and those for trunkal and facial configuration. Unusual measurements of the trunk and of the whole body were found more frequently in nondeteriorated patients, and those of the head and extremities in deteriorated patients.

FORSTER, Boston.

THE INADEQUACY OF THE EVIDENCE FOR HEREDITARY PREDISPOSITION IN EPILEPSY. EUGENE ZISKIND and ESTHER SOMERFELD-ZISKIND, Am. J. Psychiat. **95**:1143, 1939.

Ziskind and Ziskind investigated the relation of cerebral lesions to epilepsy, the incidence of epilepsy in the families of epileptic persons and the evidence of a hereditary factor in epilepsy occurring in twins. They collected the statistics on the relation of injuries to the head, and also that of tumors of the brain, to seizures, and point out that the incidence of seizures is higher in patients with lesions of the brain than in the general population and is therefore the result of the injury. They argue that histories of epileptic patients are apt to show a higher familial incidence because of interest in the illness. The controls in previous studies appear to be inadequate. Familial preponderance is not proof of heredity. In the study of identical twins the validity of the material as proof of a hereditary factor is questioned because of the possibility of other factors.

FORSTER, Boston.

THE EFFECT OF TREATMENT ON THE MENTAL LEVEL OF PATIENTS WITH GENERAL PARESIS. SAMUEL EPSTEIN and HARRY SOLOMON, Am. J. Psychiat. **95**:1181, 1939.

Epstein and Solomon point out that psychometric studies are a better criterion of improvement than the capacity to return to work. Untreated patients with dementia paralytica show a lower intelligence quotient curve than that obtained from the general population or from patients representing general admissions to a hospital. After treatment it was found that of a group of 78 patients, 45 showed no appreciable change in the intelligence quotient, whereas 22 patients showed a rise of 10 or more points and 11 showed a fall of 10 or more points. Twenty-one of the 78 patients received chemotherapy only, and the results indicate a slightly better effect in those receiving fever therapy in addition. The ability to return to work depends, at least to some degree, on the final level of intelligence. The authors believe that unless the ultimate level of 70 is reached there is virtually no opportunity for the patient to be self supporting. If a patient has a distinct drop from his preillness level to his pretreatment level, it seems unlikely that he will make a good recovery. Even if the intelligence level is high, marked delusional and hallucinatory symptoms still interfere with the results. The results showed little variation with the types of dementia paralytica, but this variation tended in favor of the euphoric grandiose patients. There is no correlation between changes in the spinal fluid and changes in intelligence. The changes in the intelligence quotient occur rather promptly, within the first months after treatment, and remain essentially constant.

FORSTER, Boston.

AGE OF ONSET OF EPILEPSY: DIFFERENCES BETWEEN DETERIORATED AND NON-DETERIORATED PATIENTS. HARRY A. PASKIND and MEYER BROWN, Am. J. Psychiat. **96**:59, 1939.

Paskind and Brown studied a group of 368 adult nondeteriorated epileptic patients who had had seizures for at least six years. The ages at onset were compared with those reported from institutions for epileptic persons. It was found that the age at onset was later in nondeteriorated patients.

FORSTER, Boston.

FREQUENCY OF SEIZURES IN EPILEPSY: DIFFERENCES BETWEEN DETERIORATED AND NON-DETERIORATED PATIENTS. HARRY A. PASKIND and MEYER BROWN, Am. J. Psychiat. **96**:65, 1939.

The authors studied 317 adult, nondeteriorated extramural patients who had had seizures for at least six years. Patients with focal neurologic signs or defective mental development were not included. The frequency of seizures in the nondeteriorated group is less than that reported for institutionalized deteriorated patients, and the authors state that major seizures occurred much less frequenly in the nondeteriorated group.

FORSTER, Boston.

ELECTRO-ENCEPHALOGRAM IN HEALTHY RELATIVES OF EPILEPTICS: CONSTITUTIONAL ELEMENTS IN "IDIOPATHIC EPILEPSY." H. LÖWENBACH, Bull. Johns Hopkins Hosp. **65**:125 (July) 1939.

Löwenbach made electroencephalograms of all the relatives of 2 epileptic patients (2 of 3 siblings). His aim was to examine as many members of the same family unit as possible, rather than a large general group of relatives of epileptic persons. Of the 37 persons without any clinical sign of an epileptic disorder, 17 showed an abnormal electroencephalographic pattern, i. e., waves which during rest were generally irregular, slow and of high and uneven amplitude and which after a few minutes of overventilation showed an increase in amplitude to exceed 200 microvolts and a decrease in frequency to 3 or 4 per second. The large slow

waves persisted in long runs for a considerable time after the period of hyperpnea. Three of the subjects exhibited outright 3 per second spike and wave groups, regarded as pathognomonic of petit mal; 1 had spike and wave groups of a higher frequency. The question is discussed whether the abnormal features are a symptom of epilepsy which is still not severe enough to take the form of convulsions or whether it is the expression of an inherited functional instability of the central nervous system and, as such, is nonspecific. From the observation of a pair of identical twins, 1 epileptic and 1 normal, the two having the same type of electroencephalograms, the author believes that the latter explanation is the more likely and that unknown factors other than the cerebral dysrhythmia have to be present in order to justify the diagnosis of clinical "epilepsy." J. A. M. A.

Treatment, Neurosurgery

FURTHER STUDIES ON THE TREATMENT OF CHOREA AND RHEUMATIC INFECTION BY FEVER INDUCTION. EDWARD L. BAUER, Am. J. M. Sc. **198**:224 (Aug.) 1939.

Bauer stresses the need for a careful history and neurologic investigation, even in the case of a very young child, before a definite diagnosis of chorea is made. From 1933 to 1936, a diagnosis of chorea was made in 85 cases, 15 of which were excluded because of a specific etiologic factor. Of the remaining 70 patients, 12 had had previous attacks of chorea, and 9 of these had cardiac lesions on admission. Ten patients gave no previous history of rheumatic infection or chorea. Twelve of the 70 patients had palpable rheumatic nodules. In 51 patients involvement of the heart was clinically evident at some time. Fever therapy was practiced with all 70 patients. Five patients were treated with diathermy, and 65, by means of 0.2 cc. of mixed typhoid-paratyphoid vaccine administered intravenously. Daily treatments for eight days constituted an average course. Speech improved rapidly after the third or fourth injection. In this group of 65 patients, 5 were given two, and 3 three, series. Fever therapy does not influence any other manifestation of rheumatic infection. Therefore patients with chorea must be subjected to such other antirheumatic measures as are available. The author's experience contradicts the reports that there is an increase in cardiac involvement in choreic persons treated with fever.

MICHAELS, Boston.

USE OF METRAZOL IN THE FUNCTIONAL PSYCHOSES. CHARLES F. READ, LOUIS STEINBERG, ERICH LIEBERT and ISIDORE FINKELMAN, Am. J. Psychiat. **95**:781, 1939.

The authors report the results of metrazol treatment of 370 persons with schizophrenic and manic depressive psychoses, 300 of the patients being schizophrenic. Of 19 patients who had been ill six months or less, all showed some improvement; of these, 42 per cent had a complete remission and 31 per cent had a social remission. In the other groups, in which the patients had been ill for longer periods, the rate of remission showed a progressive decrease, until among those ill for more than five years no social or complete remissions were obtained. No definite conclusions could be drawn as to the rate of remission for the various types of schizophrenia.

The authors believe, as a result of treating 49 manic-depressive patients, that metrazol is of some value but that it should be used chiefly in treatment of the depressions which have failed to improve. Eight patients with involutional melancholia were treated. The authors are somewhat discouraged by the results, but believe that metrazol should be tried in this condition. One patient with a severe psychoneurosis recovered.

The authors point out that the sugar, phosphorus, calcium and cholesterol contents of the blood return to their previous level in two and a half hours after injection of metrazol. Cerebral vessels were visualized in rabbits by injections

of colloidal thorium dioxide, and constriction of the vessels was noted as a result of metrazol. The authors state that the effect of metrazol is much longer than is usually thought to be the case. They do not believe that sympathetic stimulation, as shown by increase in epinephrine, is responsible for the effect.

FORSTER, Boston.

RESULTS TO DATE WITH THE PHARMACOLOGICAL SHOCK TREATMENT OF SCHIZOPHRENIA. KARL M. BOWMAN, JOSEPH WORTIS, HYMAN FINGERT and JULIA KAGAN, Am. J. Psychiat. **95**:787, 1939.

The authors report that they have obtained in a group of 28 patients who had been ill with schizophrenia less than six months a remission rate of 78 per cent. Paradoxic results have been obtained with the use of convulsants or insulin shock. Therefore the authors recommend individualized shock treatment, combining the use of insulin with that of metrazol under special conditions. FORSTER, Boston.

INSULIN TREATMENT IN SCHIZOPHRENIC PATIENTS. S. KATZENELBOGEN, HERBERT HARMS, RUTH WILLIAMS, S. BARKOFF, MORRIS W. BRODY and M. HAYMAN, Am. J. Psychiat. **95**:793, 1939.

The authors describe unusual reactions occurring in 5 patients treated with insulin shock. These consisted of prolonged coma with convulsions and improvement, prolonged coma without convulsions and with improvement and prolonged coma without therapeutic effect. They report the results of treatment in 60 patients: Thirty-five per cent had a complete remission; 8.3 per cent showed improvement, and 56.7 per cent showed no improvement. The shorter the duration of the illness the better were the results obtained. Changes were noted in the urea nitrogen, amino acid nitrogen, sugar, fermentable sugar, potassium, serum solids, phosphorus, lactic acid, leukocyte count, differential count and viscosity of the blood.

FORSTER, Boston.

INSULIN-HYPOGLYCEMIA TREATMENT OF SCHIZOPHRENIA. E. O. NIVERS, S. WEISZ and T. H. HARRIS, Am. J. Psychiat. **95**:799, 1939.

Nivers, Weisz and Harris treated 106 schizophrenic patients with insulin and report beneficial effects in 59.44 per cent. A higher percentage of remissions and a greater degree of improvement were obtained in the group of patients who had been ill for less than six months. Ninety-six of the treated patients were followed for periods of three to more than twelve months. The authors found that, although there was no demonstrable difference in the rate of recovery between catatonic and paranoid patients, the latter maintained their improvement better. They note further that patients with complete recovery showed little tendency to relapse, whereas patients with partial recovery were in considerable danger. A comparison favorable to insulin therapy is made between the 45 untreated patients used as controls and the 106 treated patients.

FORSTER, Boston.

EXPERIENCE WITH THE CAMPHOR METRAZOL TREATMENT OF SCHIZOPHRENIA. ALFRED L. C. ULRICH, Am. J. Psychiat. **95**:807, 1939.

Ulrich reports that a relapse occurred in only 3 of the 20 cases of schizophrenia reported the previous year. He then adds a group of 45 cases subsequently observed; 15 of the patients have had a social remission, and 14 are much improved. He emphasizes the need of follow-up observation for the purpose of rehabilitation and adjustment of the patient to his home environment, as well as the adjustment of the patient's family to him.

FORSTER, Boston.

SHOCK THERAPY IN SCHIZOPHRENIA. CHARLES W. MILLER JR., Am. J. Psychiat. **95**:808, 1939.

Miller studied a group of 51 patients with schizophrenia treated with shock therapy, comparing the status of the patients at the end of treatment with their condition six months later. He then compared a group of 50 untreated patients, analyzing their status after six months. A third comparison was made under similar conditions of a group of 100 patients treated with malaria. He found little difference ultimately between the groups and believes that the general opinion regarding insulin treatment is too optimistic.

FORSTER, Boston.

EXPERIENCES WITH THE PHARMACOLOGICAL SHOCK TREATMENT OF SCHIZOPHRENIA. GUY H. WILLIAMS, GUY H. WILLIAMS JR., HELEN M. KINGSBURY and DAVID E. BIXBY, Am. J. Psychiat. **95**:811, 1939.

The authors treated 75 patients with metrazol or camphor and metrazol and report improvement in 29.3 per cent, as compared with the previous spontaneous rate of 5.18 per cent in the same institution. The most serious complication encountered was the occurrence of gluteal abscesses in patients treated with camphor.

FORSTER, Boston.

EFFECTS OF VITAMIN B_1 IN SCHIZOPHRENIA. L. H. CHASE, Am. J. Psychiat. **95**:1035, 1939.

Chase states the evidence that anomalous oxygen metabolism is a factor in schizophrenia, that vitamin B_1 is associated with carbohydrate metabolism and oxygen utilization and that adequate administration of vitamin B_1 experimentally and clinically has abetted higher functions. Ten patients were given massive doses of vitamin B_1 for an average period of eight weeks. Nine patients showed no change; the recovery of 1 catatonic patient was thought to be incidental. Slight decreases were found in the levels of oxygen and lactic acid in venous blood, but no other significant biochemical changes were recorded.

FORSTER, Boston.

BULGARIAN BELLADONNA TREATMENT OF CHRONIC ENCEPHALITIS. J. B. NEAL, New York State J. Med. **39**:1875 (Oct. 1) 1939.

Neal used a white wine extract of the root of Bulgarian belladonna or tablets prepared from this extract in the treatment of 75 patients with chronic encephalitis; in most instances they had been in that stage for ten years or more. Different lots of the extract average about 2.3 decimilligrams of total alkaloids per cubic centimeter and the tablets from 3.1 to 3.5 decimilligrams. In 2 or 3 cases there was a question as to whether the parkinsonism was on an arteriosclerotic or an encephalitic basis, and in 2 there was an outstanding psychogenic factor. The patients continued to live in the same environment and under the same conditions as they previously had. They took no other drugs. No special diet was advised. It was recommended that they abstain from alcoholic beverages. Treatment was usually started with a dose of 2 cc. of the decoction, or 1 tablet, taken just before retiring. This dose was increased daily by 1 cc. of the decoction, or by 1 tablet, until there was rather marked dryness of the mouth or blurring of vision. None of the patients showed mental confusion. The optimal dose varied from a minimum of from 4 to 8 cc. of the decoction (or the equivalent of the alkaloidal content in tablet form) to a maximum of from 30 to 50 cc. Some patients prefer taking the entire dose just before retiring; others prefer to take the total dose in divided portions. It is important that these patients be under close medical supervision until the optimal dose is established and under frequent medical observation thereafter. In general, the decoction and the tablets were equally effective. Of the 75 patients, 22.67 per cent were slightly improved, 48 per cent were moderately improved and 29.33 per cent were greatly improved.

Practically all the patients showed subjective improvement. They felt stronger, were less drowsy during the daytime and rested better at night; they were less tense, more cheerful and less given to fits of depression. Objectively, there was some relaxation of the muscular rigidity. This was shown in improved facial expression, greater ease in rising from a sitting position, more normal gait and improvement in speech. In practically all cases salivation was entirely relieved. The profuse perspiration from which a few patients suffered was also diminished. While oculogyric crises usually became less frequent, less severe and of shorter duration, in no instance in the group were they abolished completely. The condition of a patient with narcolepsy following encephalitis, of many years' duration, was improved in a short time, although the results with ephedrine and benzedrine were unsatisfactory.

J. A. M. A.

TREATMENT OF CEREBROSPINAL MENINGITIS. W. J. ROCHE and C. J. MCSWEENEY, Brit. M. J. **1**:1278 (June 24) 1939.

The mortality from cerebrospinal meningitis among children at the Cork Street Hospital was approximately 75 per cent in the years in which daily spinal drainage and intraspinal serum therapy were the standard treatment. After the introduction of sulfanilamide in 1937, the mortality rate was reduced to 57 per cent. Since the introduction of sulfapyridine in the fall of 1938, the mortality has been reduced to 9.09 per cent. Eleven consecutive cases of cerebrospinal meningitis with only 1 death are reported. Six of the patients were under 1 year of age. In none of the patients treated by the new method was there hydrocephalus or other complication.

ECHOLS, New Orleans.

TREATMENT OF NERVOUS DISEASES BY VITAMIN B_1 WITH REFERENCE TO TRIGEMINAL NEURALGIA. I. BAKHSH, Indian M. Gaz. **74**:456 (Aug.) 1939.

Seven patients with trigeminal neuralgia have been treated with thiamin chloride, and Bakhsh states that in 6 of these improvement ranged from 100 (in 4) to 30 per cent. The patient who did not respond to this therapy had a history of syphilis, and although the Wassermann reaction was negative, he was given a course of mercury and iodides by mouth, without any relief. The 4 patients who were completely relieved received 160, 210, 84 and 90 mg. of thiamin chloride each; in all of them improvement commenced promptly, and in 2 it was complete when only 50 mg. of the vitamin had been given, although treatment was continued for a few days more. The author also used thiamin chloride in doses of 10 mg. daily in a case of early disseminated sclerosis for more than one month, without the slightest improvement. In another case of diabetic polyneuritis, oral and parenteral administration of from 10 to 20 mg. of the vitamin without insulin for one month produced no effect on the sensory changes; in fact, the patient complained of exaggeration of tingling and burning sensations in the hands and feet. When his urine became sugar free after insulin therapy he was relieved within a few days. In 2 cases arsenical neuritis was not influenced by prolonged thiamin chloride therapy, although similar doses in 4 cases of polyneuritis of unknown origin produced satisfactory results and the improvement was noticeable in the first week of treatment. One patient with nerve deafness did not respond to six weeks of treatment given by mouth as well as by injection. The clinical data are too scanty to evaluate the efficacy of the drug in all the diseases for which it is advocated, but it seems to be of particular value in many forms of polyneuritis. Whether the action of the vitamin is due to its replacing any deficiency or to some other action is not yet clear.

J. A. M. A.

ACCIDENTS IN THE COURSE OF METRAZOL THERAPY FOR SCHIZOPHRENIA. M. GROSS and G. GROSS-MAY, J. belge de neurol. et de psychiat. **39**:336 (May) 1939.

Gross and Gross-May discuss three groups of complications that may result from convulsion therapy of schizophrenia. In the first are the mechanical disorders which involve the osseous, tendinous and muscular systems. These are a direct result of the epileptic crisis and the enormous muscular tension which results from it. The second group are those involving the vascular system, and among these are included arrhythmia, irregularities of the pulse, auricular fibrillation and syncope. The third group are pulmonary, consisting of arrest of respiration and pulmonary embolism and abscess. These last complications may be explained by thrombophlebitis at the site of the intravenous injection, with resulting embolism, by vascular spasm due to the specific action of the metrazol or by aspiration during the attack. The authors, however, state that their enthusiasm for the new treatments for schizophrenia has not been impaired by the reports of accidents or by statistics of fatalities occurring in these treatments. In a group of 2,000 schizophrenic patients, half of whom had been treated with insulin, Malzberg found the mortality to be four times as great among the subjects who had not been treated as among those who had been treated. The authors conclude that, in view of the possible benefits, the risk entailed should not deter one from continuing with the therapy.

DE JONG, Ann Arbor, Mich.

EXPERIMENTAL INVESTIGATIONS ON SERUM THERAPY OF POLIOMYELITIS. E. GILDEMEISTER, Deutsche med. Wchnschr. **65**:1305 (Aug. 18) 1939.

Gildemeister says that in Germany the collection and preparation of convalescent serum for the treatment of poliomyelitis are arranged in such a way that serum is obtained only from those persons who have had the paralytic form of poliomyelitis. It is withdrawn at the earliest two months and at the latest ten years after the attack of the disease. The quality of these serums, that is, their content of virus-neutralizing protective substances, differs greatly, even though some equalization is produced by the mixture of several serums. Thus, there are mixed serums with good and some with deficient antibody content. Moreover, Jensen and others detected in recent years that in the paralytic forms of poliomyelitis the formation of protective substances is much inferior to that which takes place in the nonparalytic and in the abortive forms. Moreover, it has been said that high antibody contents are encountered in persons from the environment of patients with poliomyelitis and even in those who have had no contact with them. The author decided to verify these reports. He determined that storage for a year, provided of course the serum is kept under suitable conditions, does not noticeably impair the antibody content. The addition of the usual conserving substances was likewise found to be without effect on the antibody content. The author describes the method he employed in the examination of the virus-neutralizing power of four groups of serums and reports the results of his investigations. His neutralization tests demonstrated that only half of the convalescent serums of patients with paralytic or nonparalytic poliomyelitis or of the serums of persons from the environment of such patients contain noticeable quantities of protective substances, that serums of patients with nonparalytic forms of poliomyelitis had a higher therapeutic value than had the serums of patients with the paralytic forms and that serums of persons from the surroundings of patients with poliomyelitis had the least protective value. Serums from the retroplacental blood of healthy women had a surprisingly high protective value. The author concludes that the serum of patients with the meningitic forms without paralysis is best for the treatment of poliomyelitis. To be sure, aside from the unreliability of the diagnosis of the nonparalytic forms of poliomyelitis, it will be difficult, if not impossible, to secure adequate quantities of this serum. This proves that it is

necessary to continue the collection of convalescent serum from patients with the paralytic forms of poliomyelitis. However, serum from nonparalytic patients should be collected, so far as the diagnosis is certain. Only mixed serums should be used for treatment, since only mixture of a number of serums will insure the presence of protective substances.

J. A. M. A.

ELECTRIC SHOCK THERAPY FOR SCHIZOPHRENIA. G. SOGLIANI, Deutsche Ztschr. f. Nervenh. **149**:159 (Aug. 1) 1939.

In order to avoid some dangers of the treatment with metrazol and yet obtain its favorable therapeutic results, Sogliani tried electric shock therapy, which was first described by Cerletti and Bini. The apparatus which the author employs utilizes the available alternating current, which, by means of a transformer, is brought to the desired tension. The current is passed through the head of the patient by means of a hood with two metal electrodes, which are attached to the temples. The author kept the tension constantly at 110 volts and adjusted the main contact breaker in such a manner that not more than 400 milliamperes passed through. The time necessary for the production of the convulsive attack he determined in each case by first passing the current through for half a second and then, after an interval of from ten to fifteen seconds, repeating the electrical discharge for a time sufficient to elicit the convulsion. The thus determined optimal length of time which each patient required for the passage of the current in order to elicit the convulsion was subsequently employed for the elicitation of all attacks. The majority of patients required from 0.7 to 0.8 second for the passage of the current. The convulsive attacks thus elicited by electric shock are similar to those elicted by metrazol, but there are also differences in that after the passage of the current loss of consciousness results at once and the patient stretches in clonic convulsion without the cry so often heard in the metrazol convulsion. Furthermore, even in the rare instances in which an interval elapses between the passage of the current and the convulsion, the patients do not show the expression of fright and terror, with dilatation of the pupils and rigid stare, which they do at the onset of the metrazol shock. Moreover, the state of excitation so frequently seen after the metrazol convulsion is absent after electric shock. The electric shock can be repeated without danger after a few minutes. When the patient is almost regaining his consciousness, the current may be passed through again to elicit a new convulsion. In physically healthy subjects the author elicited four or five convulsions in this manner. He gives the electric shock treatment every second day. The total number of treatments required varies between five and thirty. The first favorable results are usually noticeable after from three to ten attacks, or they entirely fail to develop. Nevertheless, the author subjects every patient to at least twenty attacks, and after a certain interval he begins a new series of treatments. He reports the results he obtained with electric shock therapy of 100 patients. Of 73 patients with schizophrenia, 15 were cured, 3 improved and 55 were not benefited. This shows that the percentage of cures did not exceed that of spontaneous regressions. However, the schizophrenic patients subjected to shock therapy belonged nearly all to that group of chronic patients who neither exhibited spontaneous regression nor had been improved by other methods of treatment. Of the 27 patients with manic-depressive psychosis, 22, that is, 81 per cent, could be discharged. This high percentage is even more impressive if the duration of the disease is taken into consideration, for among those who were cured there were several who had been institutionalized for several years. In view of this fact, the author recommends the use of electric shock therapy in old cases of depressive psychosis in which other therapeutic methods have failed.

J. A. M. A.

CONTRIBUTION TO VON MEDUNA'S METRAZOL TREATMENT OF SCHIZOPHRENIA. S. NOVOTNY, Schweiz. Arch. f. Neurol. u. Psychiat. **43**:295, 1939.

Novotny reports the results of treatment with metrazol in 120 cases. The patients had all been treated since February 1937, and all, with a few exceptions, had schizophrenia. A series of courses of fever had been induced by the intramuscular injection of sulfur in oil prior to treatment with metrazol in 24 cases, during the treatment with metrazol in 3 cases and after treatment with metrazol in 21 cases. Treatment was limited to convulsive therapy in the remaining 72 cases. Though in general two convulsions a week seemed sufficient, it was necessary to increase the number to four a week in a case of catatonic stupor before good results were obtained. Of 27 cases of schizophrenia of less than six months' duration, complete remission or marked improvement followed treatment with metrazol in 74.07 per cent. Von Meduna, on the other hand, reported equally good results in 91.67 per cent of a similar series.

Preliminary treatment with artificially induced fever did not seem to enhance the effect of convulsive therapy. The induction of fever subsequent to treatment with metrazol, however, was distinctly beneficial in cases of long-standing schizophrenia in which the patients had improved to only a slight degree as the result of convulsive therapy. This was particularly true of patients who had received too much treatment, that is, those who at first improved and then became worse as injections of metrazol were continued. A marked dread of the treatment coming on after the patient had received fifteen to seventeen injections was regarded as further evidence that too many convulsions had been induced. Alternate convulsive and febrile reactions were induced in 3 cases of long-standing schizophrenia. The combined treatment was without benefit in 2 of these, but in the third case definite improvement was obtained and had persisted for eleven months at the time this paper was written. The third patient had been suffering with severe paranoid schizophrenia for eighteen years and had recently had a few spontaneous convulsive seizures.

Information was obtained relative to 39 treated patients who had been discharged from the hospital. The mental condition had become definitely worse in 5 cases, and a relapse had occurred in 7 others. The longest remission at the time of the follow-up observation was of sixteen months' duration. Treatment with metrazol seemed most effective in stuporous patients and in schizophrenic patients who were definitely depressed. The treatment also appeared to be beneficial in patients with endogenous depressions and manic states. Convulsions were induced for the relief of paranoid delusions and hallucinations in 2 cases of dementia paralytica in which treatment with malaria had been followed by serologic improvement. One patient showed slight but lasting improvement as a result of convulsive therapy, whereas the other was markedly improved at first but soon lapsed into his former delusional state.

In 2 patients aspiration pneumonia developed during treatment with metrazol. One patient died of pulmonary gangrene, while the other promptly recovered after an intravenous injection of neoarsphenamine. Since not only gastrointestinal contents but also the secretions of the upper respiratory passages can be aspirated, administration of metrazol with the patient in a fasting state does not necessarily prevent the development of aspiration pneumonia. For this reason, the author suggests that a patient receiving the treatment be placed on a hard, flat bed, without pillows, and that his head be turned to the left during the period of unconsciousness following the convulsion. A second fatality occurred as the result of an attempt to induce successive convulsions in a patient who had not improved after less drastic treatment with metrazol preceded by fever therapy. As the total dose of metrazol did not seem excessive, death was attributed to the fact that further injections of the drug were given soon after the first had been followed by a convulsive seizure.

DANIELS, Denver.

Muscular System

A Form of Congenital Myotonia in Goats. Sam L. Clark, Frank H. Luton and Jessie T. Cutler, J. Nerv. & Ment. Dis. **90**:297 (Sept.) 1939.

Clark, Luton and Cutler describe a congenital and hereditary disease in a variety of goats in Tennessee and adjacent states. When suddenly frightened, excited or faced with an emergency requiring action, these goats become hypertonic in a part or all of their voluntary musculature. When in this condition an animal can neither run nor jump, and may fall with outstretched extremities, as rigid as a wooden image. The hypertonus observed in these spasms resembles that in decerebrate rigidity, and apparently does not occur in any of the involuntary muscles. The eyes are widely opened, and the gaze is fixed. No fibrillary twitches or choreiform movements appear. Reflexes are not elicitable during the spasms, but are normal in the intervening periods. At the onset of an attack respiration is momentarily stopped, seemingly by the muscular spasm, but returns long before the limbs lose their stiffness. The heart rate is increased by from 20 to 30 per cent, but gradually returns to normal. Attacks last from a few seconds to more than a minute. Relaxation is gradual, and some stiffness in walking persists for a few steps. A period of rest and inactivity is necessary before another attack can be induced.

Studies of the chemistry of the blood in these animals revealed no abnormality in the levels of calcium, inorganic phosphate or sugar. Alterations in the level of blood sugar did not affect the spasms. Administration of large amounts of epinephrine (2 mg. per kilogram of body weight) produced marked motor restlessness and panting, lasting four hours, during which time there was no sign of hypertonus. The hereditary nature of the disease is well known to the local farmers. Breeding affected with nonaffected animals leads to dilution of the characteristic. No changes were observed in the rigidity on stimulation or removal of the cerebral cortex on one side, section of the dorsolateral part of one side of the lower thoracic portion of the spinal cord or removal of one of the cervical sympathetic trunks. Clark, Luton and Cutler compare the disease to the myotonia congenita of Thomsen.

Mackay, Chicago.

Psychiatric Studies in a Family with Myotonic Dystrophy. John F. Rittmeister, Schweiz. Arch. f. Neurol. u. Psychiat. **43**:329, 1939.

Rittmeister gives the results of psychiatric study in 6 cases of myotonic dystrophy and in 1 case of juvenile cataract without myotonic dystrophy. The first 3 patients were siblings and were second cousins of the remaining 4, who also were siblings. The clinical histories and physical findings in these cases and the results of a comprehensive genealogic survey of the entire family have been reported in detail by Katzenstein (*Schweiz. Arch. f. Neurol. u. Psychiat.* **42**:249, 1938; abstracted, Arch. Neurol. & Psychiat. **42**:944 [Nov.] 1939). The patient who did not have myotonic dystrophy was normal mentally, but the remaining 6, in contrast to other members of their respective families, showed defects of intelligence and of personality.

One patient, a woman from the first group of siblings, was a moron. A woman from the other group was likewise intellectually deficient, but the record of her progress in school suggested that dementia had been engrafted on a comparatively slight congenital defect. Of 3 patients who had made satisfactory progress in the primary school, 2, a man and a woman belonging to the first group of siblings, were dull mentally without being feebleminded; both had difficulty with problems which involved abstract thinking. The third, a man from the second group, was in general better endowed. His retention was defective, nevertheless, and in the well known problem of finding a ball in a circular field, he had great difficulty in arriving at a passable solution. This patient was better developed physically than the others with myotonic dystrophy and was more spontaneous in his reactions.

The remaining patient of the 6 who had myotonic dystrophy, a brother of the man just mentioned, had attended both the secondary and the trade schools. His performance, however, was definitely inferior, though not uniformly poor, in all tests of intellectual capacity. The Rorschach test revealed poverty of association, and it appeared from the history that development of myotonic dystrophy had been accompanied by deterioration in the affective sphere. This patient gave the impression of having a hebephrenic type of dementia.

Rorschach tests confirmed the impression that the relatively poor showing in intelligence tests of all 6 patients was due in part to deficiency of affect. The attitude and general behavior seemed to be conditioned to some extent by difficulties arising from the myotonic dystrophy. The limitation of facial expression and the generally unprepossessing appearance of these patients tended to give other persons the false impression that they were stubborn, suspicious and unfriendly. Certain authors have found patients with myotonic dystrophy to be indolent, mistrustful and shy, while others have noted mental anomalies of a more complex type, as in the cases reported here. Rittmeister observed attempts at compensation in 2 of his patients, a tendency which he believed should be encouraged. Three of the 6 patients were incapacitated economically, and it appeared that a fourth would eventually be reduced to a very subordinate position. None, however, had shown antisocial tendencies.

DANIELS, Denver.

Diagnostic Methods

CLINICAL APPLICATIONS OF ELECTRO-ENCEPHALOGRAPHY. H. H. HYLAND, J. E. GOODWIN and G. E. HALL, Canad. M. A. J. **41**:239 (Sept.) 1939.

According to Hyland and his associates, the principal clinical value of the electroencephalogram in its present stage of development, apart from the study of epilepsy, is in the localization of tumors which involve the cerebral cortex. In other organic diseases of the brain and in mental disorders the usefulness of the electroencephalogram is still limited. Gross abnormalities in the recorded waves are usually absent in the majority of cases of these conditions. Further repeated investigation is necessary, particularly in cases in which the otherwise normal "alpha" frequency is found to be below the commonly accepted normal minimum. These slow "alpha" waves, 7½ per second or less, may be seen alone or in conjunction with other slow waves. While little is known regarding their significance, there is evidence to indicate that they represent pathologic changes associated with impairment of cortical function. Here, again, future investigations doubtless will result in improved methods of recording and of the interpretation of observations, so that the value of the electroencephalogram in diagnosis may be greatly increased.

J. A. M. A.

ELECTRO-ENCEPHALOGRAM AS AID IN CLINICAL NEUROLOGY. R. A. KRYNAUW, Brit. M. J. **2**:160 (July 22) 1939.

From experience to date in the examination of intracranial tumors, Krynauw states that although the electroencephalogram is surprisingly accurate in localization in most cases, the additional help given by ventriculograms should not be dispensed with when operation is contemplated. Information as to the depth of a neoplasm, its absolute size and its relation to such structures as the ventricles and basal ganglia can be obtained at present only by adequate air studies; such information is essential in planning the scope of an operation or in deciding on the operability of a tumor. Electroencephalography alone is not a short cut to the establishment of the anatomic and pathologic diagnosis of intracranial lesions. Considerable interest is attached to the study of the epilepsies by this method. Nevertheless, it is in the epileptic group that the greatest difficulty occurs in the evaluation of results. In many cases of the type known as "idiopathic grand mal"

there is constant electrical flux, sometimes generalized and arising from the whole cortex, but often arising from one or more foci. In some cases the changes resemble closely those found in association with expanding lesions. In some cases, too, there is a tendency toward a frequent shift of the focus. These observations apply only to those cases of epilepsy in which there is a "resting focus" of electrical flux, that is, changes which can be detected between the actual fits. These changes are constant in that person and do not bear any time relation to the actual fits. There is, however, evidence that before a fit, perhaps for hours, a day or even longer, there is accession in the electrical changes. On records taken at such times appear bursts of waves of increased amplitude and varying rate, not at all unlike the "larval" attacks of petit mal described by Lennox and his associates. There are many cases in which the condition appears clinically to be idiopathic grand mal and the author has not been able to detect any abnormality of the electrical rhythm. Why this should be so is difficult to decide but from his experience there seems to be some relation between the resting focus and the cortical degeneration. In cases in which numerous minor seizures occur there are an almost constant electrical flux with occasional sudden bursts of increased activity, which have been described as larval or subclinical seizures, and then the actual petit mal attacks with even greater alterations of amplitude. The pyknolepsies are said to fall into this group. It has been claimed that in the so-called traumatic epilepsies there is never any evidence of a resting focus of electrical abnormality. The author's experience supports this, for in many cases in which fits have followed a head injury electroencephalography has yielded negative observations. However, he has records of several cases of gross localized cortical damage in which alterations of potential were observed, similar to those found with expanding intracranial lesions. In such cases he has assumed an underlying area of gliosis. In patients in whom the onset of fits occurs after the age of 40, the possibility of an expanding lesion should be ruled out, and air studies are often called for. In the author's series the electroencephalogram has always been normal when the encephalogram was normal, but further work is necessary before the reliability of the method can be assessed accurately. J. A. M. A.

Experimental Pathology

THE CHEMOTHERAPY OF EXPERIMENTAL TYPE II PNEUMOCOCCIC MENINGITIS. PAUL GROSS and FRANK B. COOPER, Am. J. M. Sc. **97**:609 (May) 1939.

Gross and Cooper produced infection of the meninges in a group of 54 rats with a 10^{-5} dilution of a culture of a type II pneumococcus, corresponding to about ten fatal doses. The fatality rate was 100 per cent in the control group (20 animals) and 60 per cent in the sulfone group (15 animals); the sulfanilamide-treated group (15 animals) showed a fatality rate of only 26.7 per cent. The initial treatments were begun six hours after the infection. A series of 45 rats were infected with a 10^{-4} dilution of the same culture, corresponding to about one hundred fatal doses. All control animals (15) were dead within sixty-eight hours, and all but 1 of the 15 sulfone-treated rats, within forty-four hours. The sulfanilamide group (15 rats) showed a survival rate of 46.7 per cent, with an average survival time of one hundred and thirty-three hours for the rats which died. Treatment similar to that in the first experiment was initiated six hours after the infection. Within less than twenty hours, 6 control and 3 sulfone-treated rats had died; they showed extensive and diffuse, but not uniformly distributed, purulent leptomeningitis of the brain and spinal cord. Sulfanilamide is suggested as an adjuvant of specific serum therapy, or as the primary therapeutic agent when such serum is not available, as a means toward an effectively lowered mortality rate for pneumococcic pneumonia and meningitis in man.

MICHAELS, Boston.

MODE OF EXTENSION AND HISTOPATHOLOGIC FEATURES OF EXPERIMENTAL TRYPANOSOMIASIS: II. MENINGOENCEPHALITIS IN DOGS DUE TO TRYPANOSOMA MAROCANUM [SOUDANENSE]. L. VAN BOGAERT, J. belge de neurol. et de psychiat. **39**:295 (May) 1939.

Van Bogaert found that meningoencephalitis due to Trypanosoma marocanum resulted clinically in dogs in general signs, such as torpor, somnolence and rapid emaciation, and in neurologic manifestations, such as paresis of the hindquarters, quadriparesis or quadriplegia, convulsions and, at times, status epilepticus. Histopathologically there was an intense, disseminated glial proliferation, involving particularly the gray matter. The lesions had no special distribution except that they were especially marked in the frontal and prefrontal cortex, the supraorbital region, the olfactory lobes and the convexity of the brain in general. There was no demyelination; the white matter was involved only by zones of infiltration with necrosis. The basal nuclei were not invaded. The cerebellum was involved at the surface of the fourth ventricle, and the gray matter of the spinal cord also seemed to be a site of choice. In rare cases there was a severe subependymal reaction with meningeal involvement. Trypanosomes were found in the cerebrospinal fluid and also in the parenchyma. The mode of extension leading to parenchymal involvement, van Bogaert believes, is secondary to meningeal, choroidal and vascular reaction.

DE JONG, Ann Arbor, Mich.

EXPERIMENTAL STUDIES ON THE SELECTIVE ACTION OF THIOPHENE ON THE CENTRAL NERVOUS SYSTEM. TEODORS UPNERS, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:623 (July) 1939.

In 1930, Christomonos noted ataxia in dogs which had been given injections of thiophene (an oily benzene derivative) during the course of experiments on the effect of organic sulfur compounds on the nitrogen metabolism of dogs. Scholz, who examined the brains of the dogs, observed changes mainly in the cerebellum, particularly in the granular layer. Upners conducted experiments to check the alleged selectivity of action of thiophene on the cerebellum. Ten dogs and 2 controls were used. Severe and mild intoxications were produced. The thiophene was not given to the point of inducing convulsions. The striking selectivity of action of theophene on the cerebellum was confirmed. The granular layer was particularly involved. In the milder intoxications there was diffuse degeneration of the cells in the granular layer. In the more severe experimental poisonings there were spotty alterations in the cerebellar tissue of the granular layer, suggesting a probable selective effect on the blood vessels. The vermis was found to be the most vulnerable part of the cerebellum.

SAVITSKY, New York.

Encephalography, Ventriculography, Roentgenography

TUMOR OF THE THALAMUS: A VENTRICULOGRAPHIC ENTITY. OLAN R. HYNDMAN and CLARENCE VAN EPPS, Arch. Surg. **39**:792 (Nov.) 1939.

Hyndman and Van Epps report the ventriculographic findings in 4 cases of tumor of the thalamus. The tumor was on the left side in 3 cases and on the right in 1 case. In the 3 cases in which the diagnosis was proved the tumor was a glioblastoma. The time from the onset of symptoms until the diagnosis was made was three, five, eight and four months, respectively. In each case the tumor was well advanced at the time the patient was seen in the hospital. The 4 patients died four, six, eleven and six months, respectively, after the onset of symptoms. While in all but case 3 one would certainly suspect a tumor of the thalamus from the clinical findings the ventriculograms left no doubt concerning the diagnosis. It is of interest that in 2 cases the spinal fluid pressure was within normal limits and that in 3 cases, including the 2 just mentioned, papilledema was not present,

or developed late. The ventriculographic pictures were all consistent and unmistakable, the two cardinal features being: (1) flattening of part 3 of the lateral ventricle (scheme proposed by Torkildsen and Penfield, Ventriculographic Interpretation, ARCH. NEUROL. & PSYCHIAT. **30**:1011 [Nov.] 1933) upward and to the ipsilateral side, which could be seen in the anteroposterior view but was more definite in the posteroanterior view, and (2) obliteration of the posterior aspect of the third ventricle and the "negative" shadow of the massa intermedia. Other features were the absence of filling defects in the contralateral ventricle, and the facts that little, if any, shift occurred in its position and that parts 1 and 2 on the involved side remained intact and the foramens of Monro unobstructed. In some cases, depending on the size of the tumor, parts 4, 5 and 6 were shifted to the ipsilateral side. The ventriculographic findings in the case of tumor of the thalamus are consistent and unmistakable and indicate an inoperable tumor.

GRANT, Philadelphia.

HISTORICAL NOTE ON THE MENINGIOMAS: I. A STUDY OF HYPEROSTOSES IN PREHISTORIC SKULLS. KENNETH H. ABBOTT and CYRIL B. COURVILLE, Bull. Los Angeles Neurol. Soc. **4**:101 (Sept.) 1939.

Abbott and Courville describe two pre-Columbian skulls which presented extensive hyperostoses similar to those currently observed in association with meningiomas. Both skulls were seen in a collection of bones in the San Diego Museum. The first, that of a middle-aged Incan, had been found near Chavina in Acari Valley, Peru, while the second, that of an elderly man, had been found on San Nicolas Island, off the coast of Southern California. The essential lesion in both cases was extensive hyperostosis over the frontal and right temporal bone, respectively, consisting of radiating spicules set perpendicularly on the surface of the skull. The spicules had fused together to form a spongy, coral-like pattern. They were loosely attached and could easily be broken off, leaving a relatively smooth outer table. Similar, less extensive growths were present on the inside of the skull. Roentgenologic examination revealed the typical radiating structure, as well as the dilated diploic channels and arterial grooves so characteristic of cases of meningioma. In the second case destructive erosion had occurred both in the external hyperostosis and in the inner table. The gradual transition from normal skull to the hyperostosis in places where no tissue had been lost suggested that the spicules developed after elevation of the periosteum. Abbott and Courville are convinced that the hyperostoses indicate the former presence of a meningioma.

MACKAY, Chicago.

Congenital Anomalies

CONGENITAL FAMILIAL EXTERNAL OPHTHALMOPLEGIA WITHOUT PTOSIS, WITH A LESION OF THE PYRAMIDAL TRACT. MAX HELFAND, Arch. Ophth. **21**:823 (May) 1939.

Helfand reports a case of congenital familial external ophthalmoplegia without ptosis, associated with involvement of the right pyramidal tract. He believes that pathophysiologic disturbances occurring between the 6 and the 10 mm. stage of embryonic development are sufficient to explain the findings in this condition.

SPAETH, Philadelphia.

HEREDITARY WORD-BLINDNESS AS A DEFECT OF SELECTIVE ASSOCIATION. WALLACE MARSHALL and JOHN H. FERGUSON, J. Nerv. & Ment. Dis. **89**:164 (Feb.) 1939.

Marshall and Ferguson report clinical studies in a case of word blindness in a college freshman, whose mother and maternal grandfather had a similar condition. The patient had compensated for his disability by substitution of auditory for visual images. Simple mathematical computations were accomplished by

"counting" on the fingers or audibly, but a difficult problem or algebra was beyond him. The authors consider speech learning as a special case of sensorimotor integration. They look on word blind persons as having failed to effect associative selection in establishing the special skills of speech, and compare them with persons who have "no ear for music." Fortunately, the word blind are frequently intelligent and compensate well for their defects. Treatment of such a condition consists of study of the patient's disability and the avoidance of difficulties for which he is especially handicapped.

MACKAY, Chicago.

STURGE'S DISEASE. A. M. NUSSEY and HUGH H. MILLER, Brit. M. J. **1**:822 (April 22) 1939.

The main features of Sturge's disease are nevi of the face and pia mater, calcification of the brain substance, epilepsy, mental retardation and glaucoma. Nussey and Miller report a case in a man aged 42 who had been mildly hemiplegic since birth. Convulsive seizures occurred early in infancy and ceased at the age of 38. He was feebleminded. A large, bluish red nevus covered the upper part of the face on the side opposite the hemiparesis. Roentgenograms of the skull showed extensive calcification of the cerebral cortex, particularly in the occipital lobe. Homonymous hemianopia was present. There was no glaucoma.

ECHOLS, New Orleans.

CLEIDOCRANIAL DYSOSTOSIS. R. DEBRÉ, M. LAMY and G. SÉE, Ann. de méd. **46**:5 (June) 1939.

Study of 5 cases of cleidocranial dysostosis disclosed that the clavicular and cranial malformations are accompanied as a rule by other malformations of the bony structure, among which pelvic malformations are the most frequent, with those of the face and spinal column following. In discussing the origin of cleidocranial dysostosis, Debré and his associates state that it is not connected with any infection, in particular not with syphilis, that it is not a bone disease of membranous origin, that it is not connected with a malformation or lesion of the uterus or the membranes of the ovum and that it is not the consequence of oligohydramnios. Cleidocranial dysostosis is a genotypic dystrophy, which seems to be transmitted as a dominant mendelian characteristic.

J. A. M. A.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

E. D. Friedman, M.D., *President, in the Chair*

Regular Meeting, Oct. 3, 1939

Presidential Address: Contribution of Clinical Medicine to Progress in Neurology and Psychiatry. Dr. E. D. Friedman.

Case of Cerebellar Medulloblastoma with Survival for Five and One-Half Years. Dr. Abraham Kaplan.

Neurologists and neurosurgeons have come to look on medulloblastoma of the cerebellum with pessimism. The prognosis for life is usually from six months to three years under the best of circumstances. It is with the hope that the outlook for this type of cerebellar tumor may become more optimistic that this case is presented. The patient not only has survived the operation five and a half years, but has led a comfortable and useful existence during this period.

History.—A Negress aged 27 came to Bellevue Hospital on April 23, 1934 because of headaches and vomiting. Her illness started with severe headaches two months before admission to the hospital. These radiated from the suboccipital region to the vertex. They lasted one or two hours and usually were made worse by sudden change in position or by straining. One month after the onset of headaches, nausea and vomiting began and were followed shortly by spells of dizziness and unsteadiness, which on several occasions were mistaken for intoxication. Soon the patient was unable to walk about. For six weeks she had noted gradual impairment in vision; since the beginning of her illness she had lost 20 pounds (9.1 Kg.) in weight.

Examination.—The patient was acutely ill, but was alert and cooperated well. Both ocular fundi showed acute papilledema, of 3 D., many flame-shaped hemorrhages and much exudate. There was only slight horizontal nystagmus and no limitation in upward gaze. The finger to nose test showed slight ataxia on the right. The Romberg test suggested swaying to the right. Visual acuity was 20/70 on the right and 20/60 on the left. The blood pressure was 95 systolic and 75 diastolic. The results of laboratory tests were all within normal limits.

Diagnosis.—Because of the scant signs of cerebellar involvement, the possibility of a tumor of the third ventricle was considered. Ventriculograms showed bilateral dilatation of the lateral ventricles and unusually good outline of the third ventricle.

Operation.—On May 21, 1934, with the patient under anesthesia induced with avertin with amylene hydrate, suboccipital craniotomy was performed. As the vermis was incised a grayish yellow tumor came into view and was removed completely. It was round and regular and measured 4 by 3 cm., having a projection at one end which had occupied the posterior portion of the aqueduct.

Histologic Observations.—Microscopic studies by Dr. Lewis Stevenson showed a medulloblastoma. The tumor was cellular, with scanty cytoplasm and rather frail connective tissue stroma. High power views showed large oval nuclei, scanty cytoplasm, a tendency to pseudorosette formation and several mitotic figures in each field.

Course.—The postoperative course was satisfactory. At the third week the patient was out of bed and able to walk; shortly thereafter she left the hospital, in excellent condition. She was given several roentgen treatments over the suboccipital region, both lateral ventricles and the entire spine. The roentgen therapy, however, made her so ill that she refused to take a complete course of treatments.

It is now five and one-half years since the operation; periodic examinations every six months show no evidence of recurrence.

DISCUSSION

DR. LEWIS STEVENSON: The interest in this case is the survival for five and a half years after operation on such a malignant type of tumor. The first question one asks is: Was this a medulloblastoma? That is certainly the first thing which Cushing would have asked in a case in which the patient had lived so long. When this type of tumor occurs in an older person rather than in an infant, the prognosis is usually slightly more favorable. The picture of the tumor which Dr. Kaplan showed indicates that he removed the entire tumor. It was solid enough to remove *in toto*. Usually medulloblastomas are what surgeons call "suckable" tumors, and cannot be removed as a whole. Sometimes Cushing thought that he had removed the entire tumor when it was solid like this, and yet in a few months it recurred. The solidity of the tumor seems to depend on the amount of stroma. Usually a medulloblastoma has a slight and very fine stroma. When I first studied this tumor under the microscope I called it a medulloblastoma; I reviewed the slides today and still think it is a medulloblastoma. It is composed of rounded cells, with little cytoplasm and a nucleus with a definite nucleolus, sometimes with two nucleoli; little stroma, and a few blood vessels.

In differential diagnosis one must consider, first, the possibility of a sarcoma. Nonmalignant sarcomas occur in the brain and can be removed without recurrence. I do not think this tumor is a sarcoma because the cytoplasm is scanty about the cells and because the stroma is not nearly as plentiful as it would be in a primary sarcoma. The stroma does not surround individual cells, as is the case in sarcoma. I cannot think of any other kind of tumor, apart from sarcoma, with which this could easily be confused. It is certainly not an oligodendroglioma. It does not have the appearance of such a tumor, and there are no neuroglia fibers. There are no fibers in the tumor which can be stained with the silver carbonate method; that corresponds with the customary idea of medulloblastoma. It might conceivably be a neuroblastoma, like some tumors that have occurred in the cerebral hemisphere and have been classified as medulloblastomas, but, in his last review, Cushing cited only 2 cases of cerebral medulloblastoma. Some of the cerebral tumors formerly diagnosed as medulloblastomas have been found by later methods of staining to be oligodendrogliomas and some to be neuroblastomas, and there were only 2 left which he considered as possibly made up of medulloblasts. The medulloblast is still a purely hypothetic cell. No one has actually identified a medulloblast. I believe that many cerebellar tumors resembling the one in the present case are derived from the granule cells of the cerebellum. The external granular layer persists until the end of the first year of life. One sees the same tendency to rosette formation in the granule cells of the cerebellum; the color of these tumors is somewhat brownish, as is that of the external granular layer, and one cannot easily demonstrate fibers in the granule cells of the cerebellum. It is likely that the cerebral tumors which have been designated as medulloblastomas are neuroblastomas. One sees in the present tumor the dividing cells, the mitotic figures, just as one sees them in the outer granular layer of the cerebellum in the infant, whether animal or human, and migrating through the molecular layer. To my mind, there is no doubt about the pathologic diagnosis in this case, as far as one is able to determine with available stains; it is one of the few cases on record that I know of in which the patient lived for this length of time. One of Cushing's patients was living thirteen years after operation, but the tumor was cerebral and was probably not made up of the so-called medulloblasts.

DR. ABRAHAM KAPLAN: I wish to thank Dr. Stevenson for his excellent discussion and for the fine histopathologic studies that he made of this tumor. In 1930 Cushing reported his experiences in 61 cases of cerebellar medulloblastomas; in only 1 instance was there a survival period of over five years. In a recent personal communication, Dr. Louise Eisenhardt stated that there are in the Brain Tumor Registry records of only 4 patients with cerebellar medulloblastomas who have survived more than five years. The survival periods of these patients are ten years, seven years and five months, seven years and five years, respectively.

Hemiagenesis of the Prosencephalon. DR. AMOUR F. LIBER.

A white boy aged 1 month died of pneumonia after three days' hospitalization. A detailed neurologic examination had not been made, although the reflexes were stated to be normal. The child had been delivered by cesarian section ten days after full term. Labor had lasted thirty-six hours, with no dilatation of the stenosed cervix. The child cried weakly. He developed "fairly well" until the terminal illness. Postmortem examination showed the head to be somewhat small, but of normal configuration. The anterior and posterior fontanels were closed. The calvarium was symmetric, but the three fossae of the base of the skull were distinctly larger on the left than on the right. The dura over the convexity on the right side was dull and brownish. The subdural space was free from blood and exudate. The subarachnoid space over the right convexity was greatly dilated and filled with gelatinous, brown fluid. The brain weighed 270 Gm. after fixation in a solution of formaldehyde. The left cerebral hemisphere measured 11 by 8 by 6 cm. It appeared normal to the unaided eye, both externally and on section. The right cerebral hemisphere was a small, wrinkled sac, measuring 7 by 4.5 by 2.5 cm. It had no recognizable gyri. The right olfactory tract and bulb were absent. The eyeballs, optic nerves and chiasm were symmetric and grossly normal. The left optic tract was well developed, but the right optic tract could be followed only a short distance. The base of the third ventricle and the pituitary gland appeared normal externally. The right pes pedunculi was extremely flattened. The right side of the pons was somewhat smaller than the left. The right anterior pyramid of the medulla was so flattened as almost to appear absent. The cerebellum was of normal configuration. The spinal cord was externally well developed. The circle of Willis and its affluent and main branches were well developed and approximately symmetric. The septum pellucidum, the fornix and the internal markings of the third ventricle were all present and symmetric. Both interventricular foramens were open. The choroid plexus in the fourth, third and both lateral ventricles was normal. The corpus callosum was as thin as paper. Internally, the right hemispheric sac was multilocular. The thalamus was small, on the right side, being about one-fourth the size of that on the left. No other central nuclei could be made out on gross inspection. Microscopically, the right hemispheric sac contained no ganglion cells. In places there was a layered arrangement of fusiform cells, often bipolar, which resembled an early embryonic mantle. Some of the cavities within the sac were lined with ependyma and in a general way followed the main subdivisions of the lateral ventricle, but were traversed by anomalous trabeculae of glia and had multiple small diverticula. Lateral to this ventricle were unlined cavities with ragged walls, which in some places merged with areas of distintegration of the tissues. In the thalamus were groups of well developed ganglion cells, alternating with areas in which there were only shrunken, often structureless, cells, or none at all. The nucleus ruber was identified, but was small and poor in cells. Scattered cells represented vestiges of the substantia nigra and the corpus hypothalamicum. The crusta was reduced to a flat glial band. In the frontal region a small nucleus of shrunken cells corresponded to the head of the caudate nucleus, but the body or tail could not be found, although the optostriate vein was observed beside the lateral end of the thalamus in many sections. The lenticular nucleus was not found. Throughout the right hemisphere were numerous foamy granule cells, both in the parenchyma

and clustered about blood vessels. There were also curious cystlike collections of small cells with clear cytoplasm and a tiny, dense nucleus, occurring as a rule near blood vessels, but just outside the perivascular spaces. Parasites were not seen. Numerous small clumps of intensely basophilic material lay in the parenchyma and in the walls of blood vessels. Stains for nerve fibers revealed that there were only scattered, very thin and generally tortuous fibers in the right hemisphere. These fibers were present chiefly in the thalamus and in the red nucleus. The only medullated fibers seen were a few small strands in the medial portion of the callosal radiation and in a small bundle ventral to the thalamus, which appeared to be the end of the lateral lemniscus. The subarachnoid space contained macrophages, lymphocytes and enormous masses of hemosiderin. The anterior, middle and posterior cerebral arteries were well developed and permeable. The apparently normal left cerebral hemisphere contained patches of disintegration, with numerous granule cells and juxtavascular cellular infiltrate and basophilic deposits similar to those observed in the right hemisphere. The anterior commissure was poor in nerve fibers. The pillars of the fornix were present on both sides, but that on the right contained only a few scattered fibers. Unfortunately, the brain stem and cerebellum were lost before they could be sectioned.

Cerebral agenesis is generally bilateral. Cerebral asymmetry is frequent, but a case of as extreme a type as the present one must be rare, since none approaching it has been found in published reports. Judging from the presence of large amounts of hemosiderin in the meninges and of disintegration of cerebral tissue in both hemispheres, it would seem that the defect was not primary. Hemorrhage and malacia had taken place. The bilaterality of the lesions and the extensive juxtavascular infiltration suggest an infection. There was no evidence of syphilis or of any other maternal infection. The mother had undergone oophorectomy and amputation of the cervix. Possibly uterine lesions had caused mechanical difficulties of adjustment of the fetus to the uterus. A remarkable feature of this case is the survival of the child for one month with so severe a cerebral defect.

DISCUSSION

DR. L. VOSBURGH LYONS: In considering the genesis in this case, one can do little more than speculate. Dr. Liber said that there may have been some degree of trauma at the time of birth, but it is hard to conceive of deterioration of that type and amount taking place during the month of extrauterine life. It seems more reasonable to suppose that the accident took place in half the prosencephalon early in fetal life. The pathologic picture is not like that due to any defect in the gene that has been described to date. It is more like an infectious process, with cellular infiltration and subsequent degeneration.

When one considers the prosencephalic derivatives that were involved in this case, one finds no cerebral cortex at all; a questionable head of the caudate nucleus, but no body or tail; considerably more of the thalamus (two identifiable nuclei, although no fiber tracts enter or leave them), and a bilaterally symmetric hypothalamus. It is obvious that the telencephalon was most involved and that the diencephalon fared a little better. This seems to be confirmatory evidence of the view that the structures of latest development from an evolutionary standpoint are the most vulnerable.

From a neurologic standpoint, the clinical record sheds little light. Neither the physicians' nor the nurses' notes make any mention of a change in reflexes or of abnormality of movement. It was noted that the child had a small head. One clinician called the condition microcephalus, and two others called it cretinism. One does not expect a child 1 month old to show much function of the pyramidal tracts, because full myelination of these tracts has not taken place. On the other hand, with the extrapyramidal system undeveloped, it is hard to speculate on what neural mechanism the child used in moving, if it did move. The left arm and leg may have been motionless, but the pediatricians may not have noted that.

About seventeen years ago, Dr. Oliver Strong obtained the brain of a child with cerebellar hemiagenesis. He obtained excellent pictures of the gross specimen and good cross sections of the brain stem up to the superior colliculi. Then, by some mysterious accident in the laboratory, the specimen was lost. In Dr. Liber's case there is something that one does not see twice in a generation, and again, through some slip, the whole brain stem has disappeared.

DR. LEWIS STEVENSON: I have read Dr. Liber's paper, examined his sections and listened to his presentation; I have considered sympathetically his misfortunes in this case, as the same kind of thing that has once or twice happened to me in my laboratory. I have come to the conclusion that this case is one of encephalomalacia with cavity formation rather than of agenesis. I think the evidence, as Dr. Liber and Dr. Lyons have pointed out, is that of a definite infection, not only in the smaller hemisphere but in the other as well. There is perivascular infiltration of inflammatory cells, which indicates clearly an infectious process, as well as the large phagocytic cells, which show that brain substance has been devoured; the meninges also are filled with these phagocytes and are somewhat thickened, though the blood vessels are normal. I can illustrate the same kind of process in an earlier stage with a lantern slide, which shows the brain of an infant who died at Bellevue Hospital at the age of 9 weeks. I have in my laboratory 5 cases of encephalomalacia in young infants with cavity formation like this, and many more cavities microscopically, as in Dr. Liber's case. This case illustrates that even in an infectious process, which was present in this case, one may have one hemisphere relatively well developed, the reason for which I cannot explain, while the other begins to show encephalomalacia with cavity formation; this is the same kind of process, in an earlier stage, as that Dr. Liber has shown. In 3 of my 5 cases of this curious disease, which is not well understood, the condition was of syphilitic origin. The mother and the child were syphilitic. It is known that the organism of syphilis can invade the fetus and cause encephalitis, with destruction of brain tissue and cavity formation. There is also evidence that mothers who have influenza during pregnancy may have children born with encephalitis which may proceed to parkinsonism; I am not sure that in all cases of encephalomalacia in infants the origin is infectious, but I think that it is in some. It is not necessarily syphilitic. Years ago, Dr. Globus pointed out in a case of porencephaly that he found definite evidence of infection in the meninges; he explained the loss of brain substance on the basis of strangulation of vessels in the pia entering the cortex. I have not been able to find any changes in the intima in my cases of syphilis; neither were there such changes in Dr. Liber's case. I do not know whether the vessels were occluded or not. I have never been able to find any occluded vessels. In all the cases of syphilis and also in those in which the condition has not been shown to be syphilis numerous phagocytes and a tremendous increase in neuroglia were shown.

DR. R. LORENTE DE NÓ: Dr. Lyons mentioned that much motion would not be expected in this infant because the central nerve fibers were not myelinated. Whether or not myelination of the central nerve fibers is necessary for function is a question that has not been studied experimentally. In this regard it may be interesting to mention work of Dr. Hursh (Hursh, J. B.: The Properties of Growing Nerve Fibers, *Am. J. Physiol.* **127**:140-153, 1939) in which he studied peripheral nerve fibers of kittens from birth to complete myelination and made the important observation that while myelination is taking place the fibers are able to conduct impulses, although at a lesser speed than in the adult. For this reason I believe that it will be necessary to revise the idea of the relation of myelination of tracts of the central nervous system to ability to function.

DR. AMOUR F. LIBER: I wish to thank Dr. Lyons and Dr. Stevenson for their enlightening discussion. There is little to add. One can only speculate as to the pathogenesis in this case. It stresses the desirability of careful clinical observation.

The "Waltzing Test": A New Labyrinthine Reaction. DR. CAESAR HIRSCH.

In this new test the subject is asked to close his eyes and extend his arms straight before him, and then to flex and raise first one knee and then the other, thereby passing from a stable into a more unstable position. The normal person is capable of performing this test not only without loss of equilibrium but also without any subjective sensation of vertigo.

If after irrigation of the external auditory canal with 5 cc. of water at a temperature of 15 C. the plane of the horizontal semicircular canal is brought into the optimum position by raising the head 60 degrees, so that the ampulla of the external semicircular canal stands above and the straight end below, the average normal person will show the first signs of deviation of the arms after approximately ten to fifteen seconds. Twenty to thirty seconds will elapse before the first signs of spinning occur. After a few more seconds the entire body of the subject begins to show postural deviation in the direction of the stimulated ear, and more pronounced waltzing movements will occur. These waltzing movements will continue as long as the stimulation of the labyrinth continues, up to 360 degrees or more.

If the position of the stimulated right labyrinth is changed so that the irrigated ear looks forward, or backward, the subject will be pulled forward or backward, but always will turn around his vertical axis, corresponding to the slow component of the nystagmus thus created.

If the head is tilted 90 degrees to the shoulder, so that the plane of the horizontal semicircular canal is in a pessimum position, no spinning or waltzing, but only swaying, is elicited.

As far as the pathologic basis is concerned, it must be stated that in a person with a dead labyrinth or with a dead horizontal semicircular canal the waltzing reaction cannot be produced. On the other hand, the waltzing reaction may easily be observed as a spontaneous reaction in persons with disturbance of equilibrium or of muscular tone. If, for instance, on stimulation of the labyrinth only falling and deviation of the arms are elicited, but no nystagmus, there exists the probability that the lesion is located in the posterior end of the posterior longitudinal bundle. Unterberger (Dreierlei neue Ergebnisse der Vestibularisforschung, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **165**:224, 1939), working with this method, has recently published 4 cases of disturbance of muscular tone in which caloric nystagmus could not be elicited, but there were deviation of the arms, falling and waltzing. Postmortem examinations showed in each case a tumor in the floor of the fourth ventricle, with destruction of the posterior part of the posterior longitudinal bundle. If nystagmus, deviation of the arms and falling, but no waltzing, are elicited, there exists the probability that the lesion lies in the vestibulospinal tract. If deviation of the arms is not produced, the other reactions being normal, the lesion is probably located in the cerebellum or the efferent pathways.

The waltzing reaction is elicited by stimulation of the horizontal semicircular canal. It is best produced by a caloric irrigation of the labyrinth with 5 cc. of water at a temperature of 15 C.

The waltzing reaction is probably due to stimulation of the homolateral vestibulospinal tracts and the change of tone in the muscles of the extremities and body. It therefore may prove to be another help in the topical diagnosis of lesions of the brain.

Spontaneous waltzing may in some cases be an earlier symptom than spontaneous nystagmus, and in many cases lasts longer. It therefore may be superior to observation of the oto-ophthalmic apparatus, because it can be observed much more easily and the reaction can be photographed in each case and thus can be kept on record much more easily than nystagmus.

The waltzing test does not inconvenience the patient.

DISCUSSION

DR. R. LORENTE DE NÓ: Dr. Hirsch's reaction adds an important complement to the technic of labyrinthine examination. The usual labyrinthine tests are

based either on ocular movements or on deviation of the arms, but Dr. Hirsch introduces a new method of testing the labyrinthine innervation that brings out in a particularly clear manner one of its most fundamental characteristics. No matter how strong the stimulation of the vestibular apparatus may be, as a rule no contraction of any muscle of the body is observed unless there is concurrent voluntary or reflex innervation. That is, although the vestibular nerve may be sending enormous numbers of impulses to the spinal cord, no motor response is produced unless a voluntary or reflex innervation is added; then, immediately, the vestibular innervation makes itself apparent and modifies the response to the voluntary or reflex stimuli. Thus, in the test of Dr. Hirsch the voluntary innervation of the muscles of the legs is interfered with by the impulses set up in the vestibular nuclei, and the patient's body rotates on its own axis.

Dr. Miles Atkinson: I have been interested in Dr. Hirsch's test. He was kind enough to discuss it with me some time ago, and it is very interesting; however, I want to cavil with him about his use of the adjective "new." When the labyrinth is stimulated by any means, the result is forced movement in certain directions, as Dr. Hirsch explained: forced movements of the eyes, of the arms and, equally, of the legs and trunk away from the axis of the body. This always occurs in a circular direction, in the direction in which the hairs on the hair cells of the ampulla are deviated, as Dohlman showed in his moving picture when he was in New York three or four months ago. When one is testing labyrinthine function in the ordinary way, one observes the forced movements of the eyes and the deviation of the arms, but one neglects usually to observe the legs, because it is inconvenient for the examiner and uncomfortable for the patient. At one time, at the National Hospital, Queen Square, London, there was in use what was called the "marking time" test, but it was given up because it failed to give any additional information. It was a lesser form of Dr. Hirsch's waltzing test. The patient was not required to hold the arms out in front; he was required merely to mark time; the patient started to rotate, as the arms rotate, always in the direction of the hairs on the ampulla. It seems to me that what Dr. Hirsch has done is to improve on that by having the arms held out so that both arm and leg movements may be observed at the same time—making the patient waltz, as he terms it. It is known that the stimulated patient will always move in a circle; if he is made to walk forward and backward, he will return gradually to his original position if the stimulation has been sufficiently prolonged and sufficiently observed. The movement is always a rotatory one on stimulation of the labyrinth. So, while it seems to me that Dr. Hirsch's demonstration is interesting, the arms being used as a lever to demonstrate the movement, it is a variation on an old theme, rather than a new tune.

Dr. Bernard Sachs: A great deal of labyrinthine work has been carried on here for years. The Bárány test has been studied carefully in clinics here for at least thirty years. I wonder whether Dr. Hirsch has selected a fortunate name for this test. All know that waltzing is a special kind of graceful movement, and I must say that I have not seen anything of the kind in the pictures shown. Perhaps some one here can help him find a better term.

Dr. Kurt Goldstein: Dr. Hirsch has demonstrated an interesting phenomenon; it would be important if it were possible to distinguish by this test between labyrinthine and cerebellar disease. As far as I can see, the turning of the standing person around his own long axis in the condition in which Dr. Hirsch brings him is one expression of deviation of the body. Such deviation is observed with lesions of the frontal lobe, of the cerebellum and of the vestibular apparatus. According to the various conditions one observes deviation to the side, deviation in a horizontal plane or deviation in the vertical plane. It may be possible that in lesions of the labyrinth the one or the other component of this deviation is more dominant, depending on whether the one or the other semicircular canal is involved; but it might also be that in dysfunction of the whole labyrinth the movement pointed out by Dr. Hirsch comes into the foreground because the experimental conditions are most favorable for this kind of movement. That

might be true also in a case of a lesion of the cerebellum or of the frontal lobe, with the experimental condition. I have not had enough experience with this test to decide whether these movements are unequivocally characteristic of labyrinthine damage. From my experience some of the patients show the rotating movement observed in Dr. Hirsch's test, but also there may be observed a circular movement if one asks the patient to go straight ahead with closed eyes. In order to discover this circular movement a sufficiently large space is required, because the amount of deviation is so slight that a clearcut circular movement appears only after a longer distance has been covered.

Perhaps the amount of rotation in the circulatory movements is different in disturbances of function of the vestibular and of the cerebellar apparatus, and perhaps this difference can become a basis for a differential diagnosis, but this has yet to be investigated on a large scale.

Dr. Caesar Hirsch: I cannot answer all the questions, but I feel impelled to say a few words in reply to Dr. Atkinson. Since Bárány established his first labyrinthine reaction, twenty-nine years ago, not much has been added to all the labyrinthine reactions; I think one should use every possible means to build up the structure of labyrinthine and cerebral diagnosis. I am particularly grateful to Dr. Goldstein for pointing out the essential nature of this test.

In reference to Dr. Sachs's remarks, all know how difficult it is to give the right name to a child; it was not easy for me to give a good name to this test.

Dr. Atkinson spoke about the "time-marking" test. I think he takes that from the English army. I was not familiar with the name; when I saw this movement I thought of the Viennese waltzes, and since the patients had been seen to revolve around their vertical axis and at the same time take steps sidewise as they do in waltzing, I chose the name the "waltzing test." I should be glad if a better term could be given; perhaps one will be found soon.

PHILADELPHIA PSYCHIATRIC SOCIETY

Baldwin L. Keyes, M.D., *President, in the Chair*

Regular Meeting, Nov. 10, 1939

Compulsive Phenomena with Associated Oculogyric Crises. Dr. Morris W. Brody and Dr. Herbert Freed (by invitation).

Two cases in which compulsive phenomena were associated with oculogyric crises are presented. In both instances the psychic state showed a transition from compulsive-obsessive to paranoid during the oculogyric crises. There was no history of antecedent causal infection in either case, and the manifestations of the so-called postencephalitis were mild. Study of the patients offered an opportunity for discussion of the underlying psychopathologic condition. This may be epitomized as a state of chronic hostility in the patient followed by formation of obsessive symptoms with added hostility and subsequent development of oculogyric crises with ever increasing expression of hatred, leading ultimately to muscle rigidity. The rigidity has both a protective and a symbolic value.

DISCUSSION

Dr. Herbert Freed: Dr. Brody and I thought these 2 cases were of interest because we had never previously seen such a sequence of events in a psychotic state accompanying oculogyric crises. We were particularly interested when the first patient had first a compulsive and then a paranoid state.

While it is usually recognized in cases of this type that an organic disorder is the predisposing factor in whatever mental states may occur, the possibility of psychic states producing manifestations of postencephalitic parkinsonism should be

discussed. To many this may seem far fetched. However, in this era of psychosomatic medicine such a possibility must be considered. That some compulsive states may have an organic basis has been proposed by Schilder. The converse is at least open for consideration as a result of our observations.

DR. PAUL SLOANE: Has any material been produced to indicate the relation of the oculogyric crises to the thought content? In many cases it seems to have been observed clinically that the oculogyric crises occur at moments that endanger the patient's life—as when he is crossing the street in traffic or when he loses absolute control of his movements.

DR. ALEXANDER SILVERSTEIN: Are the authors contending that parkinsonism may be the result of an emotional disturbance?

I saw one of the patients two years before Dr. Brody had begun to study her. She had been referred by a lawyer because of the medicolegal aspects relative to trauma. My examination disclosed a parkinsonian syndrome and a paranoid psychotic state. Reference to the hospital records of the case revealed no findings of that nature. What relation did trauma have to the parkinsonian syndrome and to the paranoid state?

DR. J. C. YASKIN: Was it suggested that the muscular rigidity considered as parkinsonism in these cases was due to the previous emotional tension?

DR. MORRIS W. BRODY: The rigidity in what seemed to be parkinsonism.

DR. J. C. YASKIN: It is assumed, then, that because the parkinsonian syndrome was preceded by emotional crises the organic neurologic condition was caused by these emotional disturbances. It seems to me illogical to assume that the presence of emotional disturbances or personality disorders in a given case of organic disease of the brain is the cause of the organic changes in that case.

I wish to cite the case of a woman, a college graduate, who was a high school teacher until seven years ago, when she suddenly began to have spells in which she felt that she had to look upward. Two neurologic examinations failed to reveal any evidences of even early Parkinson's disease. On my instruction, she came to my office during one of these spells, and I could find no evidence of an oculogyric crisis. One day I had a chance to observe her as she was entering the office and was impressed by the change in her facial expression, which was suggestive of that observed in oculogyric crises, although there was no conjugate deviation of the eyes upward. She was subjected to partial psychoanalysis for nine months; the most I learned about her was that she was the best integrated person I knew. Psychotherapy seemed to have no effect on the frequency or severity of her attacks. I then prescribed tincture of stramonium, with some benefit, and finally scopolamine, which not only aborted the attacks but, when taken after the attack was fully established, shortened its duration. This case illustrates that the patient may have organic disease of the brain, even though no definite physical abnormalities can be found.

DR. O. S. ENGLISH: It does seem a daring assumption that a mental condition which ordinarily is considered emotional or psychogenic in origin can produce symptoms that have, in the past, been thought to be due entirely to organic changes in the extrapyramidal system. It is known that emotion influences the function of the heart and the gastrointestinal system and even such deep-seated conditions as migraine, asthma and colitis. It is recognized that certain disease conditions in the central nervous system produce irrevocable changes in function. Drs. Brody and Freed have reported 2 cases and have advanced a challenging thesis; although it is a daring assumption, I believe that one can accept it and that in accepting it one is not making a wrong approach to the problem. It is possible to think of round cell infiltration in the globus pallidus and substantia nigra and to assume that the function of these areas may have been influenced by an emotional conflict. In both the cases reported there was a severe neurosis, and later psychotic symptoms. A psychosis has behind it a great deal of latent energy and latent hostility. Since emotion can affect the body in every other way, it is conceivable that it might affect posture and muscle tonus even to the point of producing demonstrable pathologic change in the extrapyramidal system.

In connection with these cases, I think of Dr. Carlson's work with spastic persons at the Neurological Institute in New York. These patients have definite injury to the brain or defective tissue structure, and integrated function is very poor. When Dr. Carlson gives these patients goals to strive for and infuses them with ambition and new emotions, their function improves greatly. It does not seem reasonable, therefore, to exclude the brain, any more than any other part of the body, from the inner relation of emotion and function.

DR. ROBERT A. MATTHEWS: So far the discussion has concerned both ends of the psychosomatic scale, but something should be said for the center. It is definitely known that emotional factors may precipitate, or pull the trigger for, symptoms in physical disease. I shall always remember a disappointed middle-aged spinster who was studied in the Philadelphia General Hospital. When the physicians made rounds, and then only, twitching of the right side of her face was noted. The chiefs and interns thought that this was psychogenic because there were no other positive findings until Dr. C. A. Patten discovered inequality of the biceps jerks. The patient died three months later of an infiltrating subcortical glioma. I am certain that the jacksonian movements were precipitated by emotional response incident to the physicians' presence in the ward. Organic pathologic changes were present, but in the early stages it required an emotional stimulus to produce an overt physiologic disturbance. The observations in the 2 cases just reported can be explained on a similar basis.

DR. MORRIS W. BRODY: In answer to Dr. Sloane's question: I think Dr. Jelliffe suggested that the eyes turn upward to heaven for forgiveness. The patient has hostility, then looks up for forgiveness.

In regard to Dr. Yaskin's statement: Three or four years ago a Rumanian physician was able to relieve attacks of oculogyric crises in postencephalitic parkinsonism with distilled water. The promptness of the response suggests that there must be a psychogenic factor.

I think Dr. Matthews is correct. When one tries to reason something out, one is apt to arrive at either one extreme or the other, while the middle is difficult to find and may be unsatisfactory.

Psychotherapy: Principles Underlying the Choice of Treatment. DR. PAUL SLOANE and DR. ELI MARCOVITZ.

In the treatment of neurosis it is important to determine what the nature of the anxiety is and whence it arises. It will usually be found to result from aggressive and erotic impulses. In psychotherapy the aim is to relieve the anxiety either by diminishing the intensity of the pathogenic impulses, short circuiting them to more socially acceptable attitudes, or by relieving the patient's guilt feelings. These aims are frequently achieved when the patient feels that he is being loved and forgiven by a father substitute in the person of the psychiatrist, and this probably accounts for the relief obtained by ordinary friendly discussion and various forms of suggestion and persuasion. Nevertheless, one finds that not all patients respond to these methods. In many instances the symptoms appear not to be touched by such superficial discussion, particularly when patients have deep-seated personality problems or character defects. If one is to gain any success or make any headway in these cases it is necessary to deal with unconscious material and to bring it to the surface of consciousness. The patient must be brought face to face with his aggressive and erotic impulses and be able to see their relationship to his anxiety, so that he may deal with them directly. It is with these persons that the question of deep psychotherapy arises.

It is a matter of experience that it is futile to probe too deeply without discrimination. A tremendous amount of time and effort appears to be wasted in aimless investigation, much of which could be spared by a judicious and thoughtful approach in which the aims and possibilities of treatment were carefully evaluated beforehand. The present paper represents an attempt to outline certain criteria by which the favorable and the unfavorable types may be recognized. These criteria consist of the ego strength of the patient, his attitude toward treatment, the nature

of his symptoms and his resources for sublimation. It will be found that they are based on the patient's desire and ability to handle his unconscious impulses and his rescurcefulness in doing something about them once they are discovered.

By ego strength is meant the ability of the patient to withstand the onslaught of his impulses and the external demands placed on him. The patient in striving to maintain a balance between his desire for gratification and his need for the affection and approval of others, begins to assume certain patterns of behavior which he is destined to follow more or less rigidly for the remainder of his life. His adjustment to life is the resultant of many forces and represents his solution of his problems and his method of defending himself, maintaining his self esteem and achieving goals in the face of difficulties. Factors which come up for consideration in this respect are the success of the patient's social, economic and marital adjustment prior to his present breakdown, his initiative and his ability to accept responsibility for his mistakes and come to grips with reality. The person who tends to project responsibility for his failures onto others, is willing to make few or no sacrifices for the sake of treatment, holds on tenaciously to his somatic symptoms and surrenders too easily or falls back onto a lower standard of living in the face of difficulties cannot be depended on to face the discomfort associated with deep psychotherapy. If the precipitating factor of his illness has been comparatively insignificant, such as failing in an examination, one may suspect that he is unable to withstand the ordinary stresses of life. Patients who become too disturbed when they are first made acquainted with their unconscious tendencies must be treated by reassurance rather than by deep interpretation, at least in the beginning. One should be wary of treating such persons on any but a superficial level. The best prospects for deep therapy are those persons who struggle to make a good adjustment and are able to assume the initiative in overcoming the effects of their illness, since they are apt to bring to the therapeutic situation the same drive for success which they have manifested in facing other difficulties in life.

Deep psychotherapy should be confined to neurotic persons. Patients with a psychosis had better be treated on a superficial level, lest one release a degree of anxiety which they will be unable to control. A person who deals with patients showing frank sexual perversions and psychopathic personalities, as well as severe obsessional and hypochondriacal symptoms, may be spared a great deal of futile effort if he will treat them superficially, since they are relatively untouched by anything short of psychoanalysis. When an urgent situation exists, such as vomiting of pregnancy, it must be handled as a real problem at once, before deep therapy can proceed. This is particularly true in the case of adolescents who are in danger of becoming engulfed by their misdirected impulses, and thus being led to commit some rash or irrevocable decision, such as leaving school, running away from home or marrying.

The patient should have sufficient anxiety about himself to want to overcome his resistance and get well, and should be secure enough not to be threatened by the personality of the psychiatrist. He must also come of his own accord and submit to the principles of treatment.

It is as foolhardy to expend a great deal of effort in breaking through the defenses and releasing the forces of the unconscious impulses in a person who cannot assimilate or reintegrate them as it is to build an elaborate structure on a feeble foundation. Treatment which liberates the patient's energies for greater productiveness is futile unless life holds something in store for him. One does not begin to dismantle a building before it has been propped up with beams, lest the entire structure collapse. Similarly, if the defensive measures which the patient has come to rely on are to be removed one must know what there is to take their place. The patient must have resources on which to fall back. The patient's reliance on the physician in the transference situation may temporarily obscure his real feeling of insecurity and create the illusion that he is strong, when in reality he cannot rely on himself. The wise physician will ask himself: "What can the patient do when he is removed from my influence and is placed on his own resources?" If the patient finds that he is left with frustrated desires and

with nothing to take their place, he may become so disturbed that the "cure" may be properly described as worse than the disease. Such a person requires other adaptations, which he may be unable to make, however, because of intellectual, emotional, social or economic limitations. It is no wonder that patients frequently counter the psychiatrist's efforts with suspicion and resentment, since to reveal their real motives might only succeed in arousing their anxiety and self dissatisfaction without enabling them to do anything about it. Such situations are exemplified by women who are restricted in their choice of social and sexual outlets and men who are frustrated economically and professionally, but who have reached a period of life when no change of a fundamental nature can be made. The most hopeful cases are those of persons in the prime of life, who are not hampered by insurmountable external difficulties, who possess ability and training and who can still hope to satisfy their sexual aspirations and succeed in social and economic spheres. In other words, the person who has something to live for will make strenuous efforts to get well and will be more willing to cooperate with the psychiatrist in deep therapy.

DISCUSSION

DR. FRANCIS J. BRACELAND: Did I understand correctly that psychotherapy is not particularly concerned in changing the patient's fundamental pattern? Did Dr. Sloane say that for prepsychotic patients—those who have difficulty in controlling their impulses—deep therapy is employed? What is a weak ego, and what is weakness of makeup?

DR. ELI MARCOVITZ: To answer most of the questions raised by Dr. Braceland another paper would be necessary. To change the fundamental pattern of a personality is, of course, a radical problem. The aim of psychotherapy, in contrast to that of psychoanalysis, is not to alter the fundamental pattern of the personality but to liberate the ego from its conflicts sufficiently to enable it to make a more efficient adjustment. This is done by relieving anxiety. Prepsychotic patients are treated by reassurance and encouragement. As a fact, one specifically avoids deep therapy in such cases, so as not to stir up unconscious material which the patient might be unable to handle.

DR. PAUL SLOANE: A weak ego is one that is not able to handle its own unconscious impulses. To avoid an involved theoretic discussion and to make the answer as brief as possible, I should characterize a person with a weak ego as a dependent person who in the face of difficulties tends to regress to infantile patterns of behavior, fall back on somatic symptoms, sink to lower living standards or project the responsibility for his difficulties onto others.

In every case of neurosis the important thing to discover first is the source of the patient's anxiety. The next step is to find out if the patient can handle the anxiety. If he cannot, there is no use in attempting deep therapy. If the anxiety comes to the surface and the patient reacts to the first reassurance that the physician offers by gaining confidence and experiencing relief from his symptoms, one has a fairly good guide as to how to proceed. Often, such patients can be dealt with superficially. The type of case which is usually perplexing, however, is the one in which the patient does not respond to such simple reassurance, or what is more, in which he continues to talk about his somatic symptoms without any display of anxiety. Before one can go ahead in such cases, one must determine whether the anxiety is too great or whether the person is too weak. The idea of this paper was suggested by the practical problem of classifying cases of neurosis for purposes of treatment.

The following case will illustrate the point I wish to make. A woman aged 29 with gastrointestinal complaints was referred to me recently. She had been treated by internists for several years and was finally said to have a psychogenic condition. When I saw her, she, of course, insisted on the organic basis of her symptoms, but was willing to consider the possibility of a psychogenic condition. On the surface she appeared to be the proper type for deep psychotherapy. She was young and attractive, had worked as a bookkeeper for a time, had lived an active social life and at one time had been a dominating and outstanding person.

During the course of treatment, however, it was observed that she evaded any consideration of anxiety-producing factors. Thus, when her hostility against her mother and her conflicts about sex were brought up, she refused to discuss them. She said: "I don't care about these things. I don't want to think that I am disturbed about sex, or that sex is a necessary part of marriage. I always want to be the way I am now, if I can be assured that I won't have any abdominal pain . . . I don't want to grow up. I am content to remain at home. I don't have to worry about the future because my father has provided for me." This attitude could have been anticipated by consideration of the patient's past life. Her illness had been going on for ten years, during which she had remained at home, avoiding all contact with reality. Here she was carefully guarded by her parents and never had to worry about material things, so that she came to have no desire or incentive to do anything about her condition. The patient's unwillingness to accept responsibility and the ease with which she fell back onto an attitude of dependency indicated a weakness of the ego which precluded deep psychotherapy. Such a patient can best be treated by reassurance. Later, perhaps, when she comes to gain self confidence from her contact with the therapeutist, deeper sources of anxiety may be touched.

Treatment of Mild Mental Disorders. DR. JAMES J. WAYGOOD.

The type of care provided in a private, so-called open sanatorium is discussed, and the advantages of such an institution are evaluated. Persons with disorders suitable for care in such an institution include: (1) patients with conversion hysteria, free from anxiety but with symptoms that cannot be cared for outside an institution because the motive for their continuance resides largely in the home environment; (2) patients with moderately severe anxiety hysteria, with many active symptoms which require nursing by persons other than relatives, in addition to psychotherapy; (3) patients with obsessive-compulsive states of sufficient severity to require removal to a neutral environment; (4) patients with mild depressions of both the reactive and the manic-depressive type; (5) An occasional patient with psychopathic personality who requires a protective environment for a time, and (6) patients with incipient schizophrenia.

A motion picture was shown covering a day in the life of a hypothetic patient.

DISCUSSION

DR. O. S. ENGLISH: The open institution has an important place in psychiatric practice, particularly for this reason: It is one of the best solutions to the problem of patients with early psychoses or certain psychoneuroses who need to be removed from the home environment—the home which for the moment I shall call conventionally psychotic. By "conventionally psychotic" I mean a home in which the attitudes toward life in general and the patient in particular are not logical, and in which the influences are not constructive for promoting the patient's recovery. All know how quickly and easily one is led to accuse another of having "crazy" ideas, but it is not usually meant that the other person is insane. Perhaps if one considers the matter frankly, one will see that any one is capable of having ideas which do not differ greatly from those of the psychotic person, the only difference being that the psychotic person has more of them and governs his life more completely by them. There are many homes in which the father or mother is overprotective of a child, an adolescent or an adult. There are other homes in which the child is overstimulated in the fields of intellectual endeavor. There are homes in which there is overemphasis on religion. Many other instances could be cited. One often hears it said that such and such a family is "crazy" to be taking such an orientation toward one of its members. When a member of such a family becomes neurotic or psychotic it is important to have him removed from those who are fostering illogical thinking or behavior which is not directed toward certain important life goals. The open sanatorium provides a place where such persons can come into contact with other human beings who will give them better ideas and a different perspective on life. This is done

by contact not only with the medical and nursing staffs but with patients who are recovering.

I feel that psychotherapy in some form needs to be further developed in the open sanatorium. It may be that group psychotherapy will find its greatest usefulness there. Some beginning with group psychotherapy has been made in other cities, but I do not know that it is being carried on to any extent in or near Philadelphia.

In an institution of this kind the rule is usually enforced that patients must not talk about themselves or their illnesses. It would seem that patients could talk about themselves, even about their symptoms and problems, constructively, provided they had guidance in doing so. In group psychotherapy much could be taught about the meaning of a neurosis or maladjustment to life in general and the patients shown how they could direct their thinking toward the future and a better adjustment, rather than have their ideas center around their present body sensations or those that existed in the past.

The extent to which group psychotherapy can be used successfully in such an institution depends somewhat on the understanding which lay people obtain of the results of a disordered, emotional and ideational disturbance. The man on the street still thinks of neuroses and psychoses in terms of something which must be treated by massage, hydrotherapy and occupational therapy rather than by gaining a better understanding of interpersonal relationships.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

R. Gordon Brain, M.D., *President, in the Chair*

Regular Meeting, Sept. 28, 1939

A Case of Essential Hypertension, with Treatment by Psychoanalysis.
Dr. Louis Adrian Schwartz, Detroit.

A case of essential hypertension is reported in which the patient underwent psychoanalytic therapy. In addition to hypertension, the patient suffered from seminal pollutions, ejaculatio praecox, anxiety and a cardiac neurosis accompanied by precordial distress, tachycardia and extrasystoles. The analysis was terminated after the patient had remained free from symptoms for over two months.

The conflict situation showed the classic picture recently described by Saul (*Am. J. Psychiat.* **95**:1449 [May] 1939), namely, a masochistic submissive and oral dependent attitude toward a dominating mother, leading to a masochistic submissive attitude, a rigid superego and, homosexually, a deep attachment to the parent of the same sex. Further, there developed chronic, unsuccessful, unsatisfied rebellion and hostility in protest against this submission. The rebellion and hostility were conscious, or near to consciousness, but were not expressed directly because of fear of loss of love. The masochistic homosexual submissiveness was not conscious, and bitter hostility opposed its being made conscious in the analysis. Another prominent feature was excessive fear of heterosexuality, which was to some extent indulged in despite the anxiety. The crucial point for the hypertension seemed to be the hostile rebellion against the masochistic submissiveness, with consequent anxiety.

The patient was masculine looking, used sexual promiscuity and alcoholism as outlets and showed the chronic rebelliousness particularly in relation to his superior in his work situation.

The case, then, suggests that hypertension may be associated with long-continued repressed hostility and rage, with the consequent production of constant

conflict which the patient can neither escape nor solve. Therefore, in the condition of essential hypertension, too, as Virchow has aptly stated, "We must treat not only the disease, but also the patient." Such treatment necessarily involves an evaluation of the patient's personality and emotional development, as seen in historical perspective.

DISCUSSION

DR. RICHARD STERBA, Detroit: This paper is concerned with the borderland between the psychic and the somatic. I shall take the liberty of adding some methodologic considerations of a general nature, starting with the question whether it is justifiable to regard psychologically certain somatic diseases which until now have been entirely the domain of somatic medicine, and to undertake to influence them psychotherapeutically. The psychic treatment of organic disease is not new; it is as old as the art of medicine itself. From the magical practices of the primitive medicine man and the superstitious practices of the Middle Ages and of modern times to the healing methods of Christian science, one finds unremitting efforts on the part of mankind to influence the diseased body by the mind. It is certainly justifiable that science should concern itself with such therapeutic endeavors and should investigate them, determine their truth and develop for the benefit of sick mankind all that which can stand the severe test of its objective examination.

I should like to consider this question: Which concepts of the psychoanalytic theory can be used to approach the problem of organic disease? There are two fundamental concepts in psychoanalysis which can be considered as methodologic possibilities in approaching this problem. The first is the concept of the instinct. Instinct is a term with a Janus head, as Freud said; it is a psychophysical concept, one part of which concerns the organic, the other the psychic, sphere. In the psychoanalytic theory of instincts, which is the basis of psychoanalysis, this borderland concept, as Freud called it, is continually in use as an explanation, the psychologic findings being thus given a biologic foundation. In this way, psychoanalysis becomes a combined science of the physical and the psychic, the psyche and the soma being regarded as two aspects of a biologic unity. When one tries, in psychoanalysis, to explain psychic disturbances through instinctual drives one is explaining psychic phenomena as originating in the organic sphere because, in the psychoanalytic concept, instincts arise from somatic sources. It is scientifically justifiable to investigate organic disease by means of the same borderland concept of instinct, as the somatic is only one aspect of the biologic unity, the soma-psyche.

The second concept which one may use as an approach to this problem is the concept of conversion, which has already become common property to psychiatry. The term conversion means that under conditions of neurosis psychic contents are expressed in physical symptoms, with partially demonstrable organic changes, generally of a vascular nature. It is a legitimate undertaking to investigate to what extent organic diseases can represent a wider form of conversion.

In the case of certain somatic diseases, such as asthma, some forms of allergy and ulcus ventriculi, there is no doubt as to the psychic origin, but with regard to others one must wait for further experience.

If I, who have lived for many years in personal and scientific contact with Sigmund Freud, were to be asked what attitude it is wisest to take toward the efforts and results of psychosomatic investigation, I could recommend only that which I have repeatedly observed Freud himself to take during discussions on the subject. Freud characterized his attitude toward the psychotherapy of purely organic illnesses as one of benevolent skepticism. This skepticism consists of collecting observations, of taking relevant ideas into consideration, of testing them and of waiting until time has verified the knowledge. Science has "oceans of time"; nothing compels it to a hasty judgment. Science is not bound up with the short life of a single human being, but exists in a continual flow and interchange of ideas, and can therefore afford to wait till experience leads to an ultimate judgment.

The Unconscious. Dr. J. Clark Moloney, Detroit.

To illustrate the importance of the dynamics of the unconscious, a report is given of the psychoanalytic findings in the case of a police officer aged 28, particularly as obtained from the dream material related by the patient. Of particular note were his exhibitionistic and destructive aggressive trends, his extreme feelings of inferiority and his criminalistic tendencies. The analysis, which is as yet incomplete, has effected a marked improvement in his social and economic adjustments.

DISCUSSION

Dr. Leo H. Bartemeier, Detroit: Jones (Paper on Psychoanalysis, ed. 4, Baltimore, Williams & Wilkins Company, 1938) stated that it is one of the fundamental principles of the psychology of Freud "that psychical processes are never isolated or accidental phenomena, but that they are as precisely related to preceding and succeeding ones as are successive physical events. Freud therefore looks upon the whole of the subject's mental life as a continuity, as a series of associated trends." Another important principle in freudian psychology is that "the mental processes, and particularly the wishes, of early childhood life are the permanent basis for all later development. Unconscious mental life is indestructible and the intensity of its wishes does not fade. Wishes and interests of later acquirement are chiefly significant in so far as they ally themselves with those of childhood life. A great number of reactions of adult life owe their real force to the adjuvant impulses contributed by the unconscious."

Dr. Moloney has demonstrated clearly the existence of these two principles in the partial presentation of his study of this patient. He has sensed accurately that this man was entirely ignorant of the real motives which prompted him to become a policeman, and he has described how the patient, without any awareness of what he was doing, attempted to solve his various mental conflicts in his work. The occupation of policeman appealed to him because it offered gratification of one group of strivings and because it aimed to protect him from still other repressed trends of which he was obviously afraid.

As I read the paper I was impressed by the fact that this man, in attempting to defend himself against those urges which were so wholly unacceptable to him and which were always threatening to break through into his conscious life, had selected an occupation which was beyond his capacity. It is possible that if he had selected work which made lesser demands on him he could have solved his problems more adequately. Dr. Moloney has demonstrated this in the part of his paper in which he shows how the role of policeman was out of proportion to the large infantile nucleus in this man's personality.

I deem it important to recall that Freud's discovery of the unconscious was not accomplished suddenly. He arrived at his conception of the nature of unconscious processes, their content and their meaning only through a period of years. He established his conclusions by strictly scientific methods, with a wealth of clinical material. His employment of the technical procedure of free association was an especially tedious process. It continues to be tedious, and the unconscious must be rediscovered in each person undergoing psychoanalytic treatment.

The division of the mind into conscious and unconscious portions begins extremely early in the life of every person. It undoubtedly commences well before the second year. This fractioning of the psychic apparatus is accomplished by the process of repression—an activity which operates automatically, without the awareness of the person, and which functions unceasingly throughout life. It is the task of the repressing forces to prevent the various unconscious processes which are incompatible with social and moral standards from entering consciousness. These processes, which are described as wishes, are always seeking gratification, and the inhibiting forces of repression are often not effective barriers.

The neurotic symptom, which was previously so meaningless, is now understandable as a compromise evolved out of the conflict between impulses which are unacceptable to consciousness and the influences operating against their expression. Knowledge of this sort not only is of prime importance for pathology but is also indispensable for any really effective therapy of neurotic disorders.

Book Reviews

Problems of Ageing: Biological and Medical Aspects. A Publication of the Josiah Macy Jr. Foundation. E. V. Cowdry, Editor. Pp. 758. Baltimore: Williams & Wilkins Company, 1939.

Volumes on one subject, bringing together reviews and new data from various investigators, have a great usefulness in these days of surfeited publication. The present book logically follows that on "Arteriosclerosis" published by the Macy Foundation in 1933. The book has 758 pages and is divided into 25 chapters, each by a different man. The contributors are well chosen, many of them being eminent in their field.

The chapters of especial interest to neurologists are those by G. V. Hamilton on "Changes in Personality and Psychosexual Phenomena with Age," by M. Critchley on "Ageing of the Nervous System" and by W. R. Miles on "Psychological Aspects of Ageing." Hamilton's chapter gives an unusually clear exposition of psychosexual development from infancy to senility. He summarizes by saying:

"Evaluations of the psychosexual phenomena and personality changes observed in ageing persons cannot be adequately made without reference to all of the four major turning points recognizable in a total life span, which includes a period of involution. These are: (1) The termination of psychological infancy and the beginning of childhood.

(2) The termination of childhood and the beginning of adolescence.

(3) The transition from adolescence to maturity.

(4) The period during which the personality changes from a matured to an ageing structure.

"The findings of psychopathology show that most of the somatically conditioned changes or newly established trends in modes of personality function which mark the first, second and third of these turning points are reversible processes. This appears to be also true of the fourth turning point.

"Clinical studies of ageing persons suggest that, before extreme old age is reached, lack of educability, impairment of memory for recent events and marked increase of intolerance and conservatism are escapable developments.

"The traditional assumption that men and women typically experience a climacteric which marks a critical decline in sexual potency and desire remains a debatable one. Clinical observations disclose the fact that these symptoms can appear as psychical reactions to physiologically conditioned reduction of sexual potency.

"Detailed studies of psychosexual and related forms of regression in ageing persons disclose the importance of frustration as a factor involved in the appearance of such phenomena. Disabilities of a primarly somatic nature, social and other environmental handicaps and unconscious psychical interferences carried over from earlier life make for frustration of adult types of sexual impulses which still arise in elderly persons, and tend to throw them back upon the autoerotic and pregenital satisfactions of infancy."

Concerning the common disturbances of memory of elderly persons, it is comforting to find that Hamilton is not fatalistic. He believes that "we must take into account the fact that external circumstances and more subtly operative subjective factors often make for a marked change in the preoccupations of ageing persons. The patronizingly protective attitude of younger adults toward elderly ones, the steadily increasing physical debility that goes with ageing and the common expectation that after sixty the individual's practical usefulness is nearing its end, make for a sense of inadequacy and a consequent withdrawal of attention

from various details of present external realities. It may be, then, that since memory is importantly a function of attention, many ageing persons are more forgetful of recent events than need be."

Professor Miles, in chapter 20, discusses the more measurable psychologic factors. Despite his somewhat confusing mysticism concerning the mind-body relationship, he presents much important information in an interesting way. Like Hamilton, he is optimistic about old age; he agrees with Emerson's dictum that the essence of age is intellect. He shows that between the ages of 20 and 65, chronologic age alone is not a guide to intelligence. Formulations regarding life goals and evaluations of ability to organize energy to achieve these goals make a better basis for intellectual classifications than scores in intelligence tests. In the data gained from the life work it is shown that the best work of essayists, physicians, statesmen, philosophers, astronomers, mathematicians, historians, jurists and naturalists is done at an age over 50. Thus, the absurd but widely accepted generalization of Osler that important human achievements are almost entirely the work of men under 40 is satisfactorily controverted. Psychologic factors of ageing include and depend on a completely demonstrated physiologic regression, but the range, at every age, of individual differences in capacity is many times larger than the year to year age decrement. Success is a function of individual personality. The more it involves experience and considered judgment, the more it is resistant to psychophysiologic age deterioration.

As regards physiologic deterioration, Cannon states in chapter 22: "The condition of the homeostatic mechanisms in old age can be summarized in the statement that when subjected to stress they are revealed as being more and more narrowly limited in their ability to preserve uniformity of the internal environment of the living parts."

Critchley, in 13 somewhat hasty pages, undertakes to discuss the "Ageing of the Nervous System." Gross changes comprise thickened meninges, hypertrophied arachnoid villi (pacchionian granulations) and even calcification and ossification in the meninges. Cerebral atrophy is common, with loss of weight of the brain; the white matter is more atrophied than the gray, which is darkened. The ventricles are widened, and the ependyma is granular.

Microscopic examination shows that the nerve cells are reduced in number, especially in the third lamina of the cortex. The cells themselves are somewhat reduced in size and have an excess of pigment (lipoid or iron). The neurofibrils are thickened and take up silver in excess; they often form coarse bundles, tangles and coils (Alzheimer's fibrillary change). There is glial overgrowth as well as regressive changes in the oligodendroglia and microglia. Corpora amylacea are numerous in most senile brains, and are seen lying around the blood vessels, under the pia and especially about the cornu ammonis. Free iron may be found in perivascular spaces, usually of the globus pallidus. Senile plaques are scattered throughout the cortex in the deeper layers; they are made up of microglia cells and fibers and substances of amyloid nature. In the spinal cord there are decrease in number and pigmentary degeneration of the ventral horn cells, especially in the upper cervical segments; the lateral horns are free from changes (a notable fact in relation to the freedom from senile change of autonomic nuclei in the cerebrum). Myelin sheaths show patchy degeneration.

From the clinical standpoint, one observes progressive loss of vibratory sense and diminished pupillary reactions, ankle jerks and abdominal reflexes. Plantar reflexes are equivocal, and occasionally extensor responses are obtained. There is a generalized slight poverty of movement, with slowness and lack of ability to relax. The gait is characterized by marche à petits pas. There is a fixed and bowed stance with impressive features. Senile tremor is somewhat rare.

The senile psychoses are those that are characteristic of advanced life. Senile dementia and arteriosclerotic dementia are considered as distinct entities. Pick's disease is looked on as a late heredodegeneration, not a form of arteriosclerosis. Alzheimer's presenile psychosis, although clinically much like Pick's syndrome, has a specific pathologic picture. "The ageing of the nervous system takes place

independently of degenerative changes of the cerebrospinal blood vessels. Although both types of change are commonly present in association, there is probably no direct causal relationship between arteriosclerotic and cerebral involution." The reviewer finds it difficult to agree with the last statement. The supposition that "a man is as old as his blood vessels" does not seem to have been disproved. Diffuse lessening of oxygen supply to nerve tissue might take place without obvious arteriosclerosis. Moreover, most of the symptoms of senility described by Critchley might be placed in two syndromes, reminding one of (*a*) paralysis agitans and (*b*) subacute combined degeneration of the spinal cord. The question might be asked whether slowly progressive changes in the basal ganglia, as well as mild degenerative processes affecting the cord, are not almost universal in old age. Whether deficiency of blood, oxygen and vitamins plays a role is for future research to decide.

The book is well organized and illustrated. References and indexes are adequate. One wishes the proofreading had been better, for many misspellings appear. But, despite minor faults, the book is a great piece of work and a valuable addition to any medical library.

The Genetics of Schizophrenia. By Franz J. Kallmann, M.D., and Senta T. Rypins. With introduction by Nolen D. C. Lewis. Price $5. Pp. 291, with 81 tables. New York: J. J. Augustin, Publisher, 1938.

Dr. Kallmann began this important work under Professor Rudin at the German Research Institute for Psychiatry in Munich. The material was gathered in Berlin in 1929, but the coordination of data and the assembly of the book had to be postponed several years, since political developments in Germany closed to him the possibility of completing his research there. The authors insist that the field must be considered an exclusively medical problem dealing only with biologic facts. It should not be confused by philosophic considerations or complicated by political speculations and prejudices. Pretexts advanced against eugenic prophylaxis are palpably insincere in a population which already practices birth control extensively for economic and social reasons.

The total group of families in the study embraced the kin of all schizophrenic patients admitted to a hospital in Berlin between 1893 and 1902 whose clinical records were still available in 1929. Altogether it covered 1,087 schizophrenic "probands" (the original objects of investigation) with their 3,279 parents, husbands and wives, 3,384 direct descendants, 3,920 brothers, sisters, half-brothers and half-sisters and 2,194 nephews and nieces. The material was divided into four diagnostic groups: patients with hebephrenia, those with catatonia, those with paranoid schizophrenia and those with "simple schizophrenia," so called in consideration of its mild and episodic course.

A distinction manifested itself clearly between the hebephrenic and catatonic patients, on the one hand, and the paranoid and simple schizophrenic patients, on the other; these are named the nuclear and the peripheral group, respectively. In a quantitative study the significant finding is that the birth rate is much lower in the nuclear than in the peripheral group. Of equally striking importance is the fact that the total fertility is much below that of the general population. The hebephrenic and catatonic patients marry only about half as frequently as the general population and have, on the average, only a little more than one child; however, only 30.2 per cent of all the children were born after the parent's first internment in an institution. Hence, only one third of all the children could have been eliminated by sterilization of the diseased parent at the onset of his psychosis. Among the paranoid patients the situation was even worse; 96.2 per cent of all children of paranoid men were born before the commitment of the parent to an institution.

"For eugenic purposes, it is sufficient that schizophrenia has been proven an *organic* disease based on a *specific* predisposition which follows the recessive course of heredity and is therefore transmitted to all the children of schizophrenics.

It is too often forgotten that only predispositions are inherited and never attributes as such, and that the phenotypical manifestation of the trait in the individual depends on the sum of all the given environmental conditions.

"The total figures for the probability of schizophrenia, according to the abridged method of Weinberg, are 16.4 per cent for the children of our probands, 11.5 per cent for the siblings of probands, 7.6 per cent for half-sisters and half-brothers, 3.9 per cent for nephews and nieces and 4.3 per cent for grandchildren. The children of schizophrenics have thus a probability of schizophrenia about nineteen times as high as the average population, while the grandchildren as well as the nephews and nieces are still about five times more likely to develop schizophrenia than the average person.

"Conversely, the probability of schizophrenia increases enormously in the offspring of two schizophrenic parents. When we include all children descending in our various generations from such parents, we obtain an expectancy of 68.1 per cent. This rate corresponds perfectly with the percentage found by Rosanoff and his collaborators for the concordance of schizophrenia in identical twins (68.3 per cent). Both figures prove definitely, despite Rosanoff's reserve in evaluating his findings, the heredity of schizophrenia and the recessive course of its transmission, and indicate particularly that in about 30 per cent of homozygotic taint-carriers the manifestation of the predisposition to schizophrenia is inhibited by certain somatic processes or by the lack of furthering dispositional factors."

The inheritance seems to be completely independent of the sex of the schizophrenic parent; there are no differences in the expectancy figures for the children born before or for those born after the onset of the disease in the parent. The probability of schizophrenia in the offspring is affected by the biologic character of the wife or husband only insofar as that parent may be tainted with the same predisposition, and, if so, by whether he is a homozygotic taint-carrier or merely a heterozygotic type. The specific character of the predisposition to schizophrenia is indicated by the fact that only symptoms of the schizophrenic syndrome appear in descendants. There is no increase in other psychopathic traits.

The authors' data are convincing and should be taken seriously by all students of psychiatry. The plea that one should consider schizophrenic symptoms without inherited taint as "schizordia," not as "genuine schizophrenia," seems a bit difficult to live up to in view of the fact that the disease is recessive and may not always become apparent even in the homozygotic carriers. At the end of the book there is a discussion of the remarkable similarity of the inheritance of tuberculosis to that of schizophrenia. The conclusion is that both are due to a "hereditary functional weakness of the reticuloendothelial system." The reviewer's impression is that this part of the work is not so thoroughly carried out and does little but weaken the impressiveness of the book as a whole.